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SECTION 7

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Second Cancers

Modern chemotherapy and radiotherapy have increased substantially the survival of patients with cancer. In particular, cure rates have shown dramatic improvement for patients with Hodgkin's disease, testicular cancer, and pediatric malignancies. Less impressive, but nonetheless convincing, improvements in survival also have been achieved for patients with breast cancer, non-Hodgkin's lymphoma (NHL), and several other tumors. Now that substantial numbers of cancer patients experience such a favorable prognosis, it becomes increasingly important to evaluate the long-term complications of treatment. Because the survival benefits associated with modern treatments have been greatest for those cancers that occur at relatively young ages, cured patients are subject to long-term side effects, which may not emerge until several decades after treatment. Paradoxically, research conducted since the late 1970s has clearly demonstrated that some of the modalities used to treat cancer have the potential to induce new (second) primary malignancies. Of the many late complications of treatment, second cancers are generally considered to be the most serious, because they not only cause substantial morbidity but also considerable mortality. For example, among 15-year survivors of Hodgkin's disease, second cancer deaths have been reported to be the largest contributor to the substantial excess mortality that these patients experience.[1] Increased risks of second cancers have been observed after radiotherapy, chemotherapy, or combined modality treatment.

In any discussion of treatment-related second malignancies, it is of primary importance to remember that not all second cancers are due to therapy. The occurrence of two primary malignancies in the same individual may reflect the operation of numerous influences. Multiple primary cancers may result from host susceptibility (genetic predisposition or immunodeficiency), common carcinogenic influences, a clustering of risk factors, treatment for the first tumor, diagnostic surveillance, a chance event, or the interaction of these factors. In view of the high prevalence of cancer in the general population and the increasing incidence of most cancers with age, it is important to exclude the role of chance in the development of second cancers. To this end, comparison with cancer incidence statistics derived from the general population is crucial. If a second malignancy is demonstrated to occur in excess, the contributions of other risk factors need to be ruled out convincingly before the increased risk can be attributed to treatment. The temporal trend of excess second cancer risk may provide an important initial clue to etiology; for example, the risk of solid tumors after radiotherapy generally increases with time since exposure. The evaluation of the carcinogenic effects of therapy, however, is complicated by the fact that therapeutic agents are frequently given in combination. Appropriate epidemiologic and statistical methods are required to quantify the excess risk and to unravel the role of treatment and other factors.

Whenever interpreting results of second cancer studies, it must be kept in mind that the problem of treatment-induced malignancies has arisen by virtue of the success of cancer therapy. As more becomes known about the influence of various treatment factors on second cancer risk, therapies may be modified to decrease the risk while maintaining equal levels of therapeutic effectiveness.

The major aspects of second malignancy risk in relation to cancer treatment are addressed in this chapter. After a discussion of methods used for the assessment of second cancer risk, an overview of the carcinogenic effects of radiotherapy and chemotherapy is presented. Subsequently, the risk of second malignancies after treatment for Hodgkin's disease, NHL, testicular cancer, breast cancer, ovarian cancer, and pediatric malignancies is reviewed. Emphasis is on large studies that have been published most recently.

METHODS TO ASSESS SECOND CANCER RISK

Estimates of second cancer risk after treatment of various primary malignancies derive from several sources, including population-based cancer registries, hospital-based cancer registries, or clinical trial series.[2] The epidemiologic study designs generally used are the cohort study and the case-control study.

In a cohort study, a large group of patients with a specified first malignancy (the cohort) is followed for a number of years to determine the incidence of second cancers. To evaluate whether second cancer risk in the cohort is increased compared with cancer risk in the general population, the observed number of second cancers in the cohort is compared with the number expected on the basis of age-, gender-, and calendar year–specific cancer incidence rates in the general population. The analysis takes into account the observation period of individual patients (person-years).[3] The relative risk of developing a second cancer is estimated by comparing the ratio of the observed number of second cancer cases in the cohort to the number expected. When the relative risk is increased, the question arises as to whether the excesses are due to therapy. This issue can be evaluated by comparing risks between treatment groups, preferably within specified follow-up intervals and, when possible, with a reference group of patients not treated with radiotherapy and chemotherapy. Second cancer risk in the cohort (and in different treatment groups) can also be expressed by the cumulative (actuarial estimated) risk,[4] which yields the proportion of patients alive at time t (e.g., 5 years from diagnosis) who can be expected to develop a second malignancy. When the cohort's death rate due to causes other than second malignancy is high, the assumptions underlying the actuarial method may not be valid, and competing risk techniques should be considered to estimate cumulative risk.[5,6] Because many treatment-related cancers are rare in the general population (e.g., leukemia, sarcoma), a high relative risk (compared to the population) may still translate into a rather low cumulative risk. Absolute excess risk, which estimates the excess number of second malignancies per 10,000 patients per year, perhaps best reflects the second cancer burden in a cohort. This risk measure is also the most appropriate one by which to identify those second malignancies that contribute the most to elevated risks.

Each of the data sources used to construct a cohort has its own set of advantages and disadvantages. Population-based cancer registries frequently have large numbers of patients available, which allows the detection of even small increases in the site-specific risk of second cancers.[7] An additional advantage is that the observed and expected numbers of cancers derive from the same reference population. Disadvantages of this approach include the limited availability of treatment data, underreporting of second cancers[8,9] (in particular hematologic malignancies and bilateral cancers in paired organs), and different diagnostic criteria for second cancers. Population-based registries differ greatly in these aspects and, hence, in their usefulness for second cancer studies. If treatment data are not available, it is impossible to determine whether excess risk for a second malignancy is related to treatment or to shared etiology with the first cancer. Despite their disadvantages, population-based registries are especially well suited to broadly evaluate which second cancers occur in excess after a wide spectrum of different first primary malignancies. They also provide a valuable starting point for case-control studies that evaluate treatment effects in detail (see later in this section).

A major strength of clinical trial databases is that detailed treatment data on all patients are available. Comparison of second cancer risk between the treatment arms of the trial controls for any intrinsic risk for a second malignancy associated with the first cancer. Limitations of most trials include the small number of patients involved and the frequent lack of data on subsequent therapy. The dearth of large numbers becomes more serious when the second cancer of interest has a low background incidence (e.g., leukemia). Furthermore, the end points of interest in the majority of clinical trials include only treatment response and survival, not the development of second cancers. Therefore, many clinical trials do not routinely collect information on second malignancies, and some do not collect any data beyond 5 years. Routine reporting and assessment of second malignancy risk should become an integral part of clinical trial research.[10]

Many large cancer treatment centers maintain registries of all admitted patients. Most of these registries have been in existence for decades and collect extensive data on treatment and follow-up. As compared with trial data, hospital registries provide larger patient numbers and a wider variety of treatments and dose levels, which may yield important information on drug and radiation carcinogenesis. Most studies of second cancer risk after Hodgkin's disease have been based on data accrued from hospital registries.[11–13]

The cohort study is not an efficient design when examining detailed treatment factors (e.g., cumulative dose of alkylating agents) in relation to second cancer risk. Most cohorts are fairly large (to yield reliable estimates of second cancer risk), rendering the collection of detailed treatment data for all patients prohibitively expensive and time-consuming. In such instances, the so-called nested case-control study within an existing cohort is the preferred approach. The case group consists of all patients identified with the second cancer of interest, whereas the controls are a matched sample of all patients in the cohort who did not develop the cancer concerned, although they experienced the same amount of follow-up time. Matching factors typically include age, gender, and calendar year of diagnosis of the first cancer. Even when the control group is three times as large as the case group, detailed treatment data need only be collected for a small proportion of the total cohort. In each case-control investigation, it is critical to the validity of the study that the controls are truly representative of all patients who did not contract the second cancer of interest. In data analysis, treatment factors are compared between cases and controls, and the risk associated with specific therapies is estimated relative to the risk in patients who received other treatments. The cumulative risk of developing a second malignancy cannot be derived from a case-control study. Treatment-specific absolute excess risks can be estimated, however, when the case-control study follows a cohort analysis. Although case-control methodology has not been applied to the investigation of second cancer risk for a long period,[14,15] several landmark studies have already demonstrated its strengths.[8,16–22]

CARCINOGENICITY OF INDIVIDUAL TREATMENT MODALITIES

RADIOTHERAPY

The carcinogenic potential of ionizing radiation was first recognized in the mid-twentieth century,[23–25] and comprehensive reviews have now been published.[26–28] Much of the data with regard to radiation effects in humans has derived from epidemiologic studies of the atomic bomb survivors in Japan,[29–32] occupationally exposed workers,[33,34] patients given large amounts of diagnostic radiation,[35,36] and patients treated with radiotherapy for malignant[16,19,37–39] and nonmalignant diseases.[40–44] Most types of cancer, with the exception of chronic lymphocytic leukemia, can be caused by exposure to ionizing radiation.[26,30,45] Boice et al.[28] have ranked various body tissues with regard to cancer induction by radiation; certain sites, such as the thyroid, female breast, and bone marrow, clearly are more radiosensitive than others.

The excess risk of leukemia attributable to irradiation is observed within a few years after exposure, with a peak at 5 to 9 years, and a slow decline thereafter.[16,27,30,40,41] Some controversy exists as to whether, and when, leukemia risk decreases to background levels in the population.[16,30,41,46,47] In the atomic bomb survivors, risk declined more rapidly for those exposed earlier in life.[30] Increased risks of solid tumors have been shown to emerge much later. After a minimum induction period of 5 to 10 years,[12,13,37,40,41,48] solid tumor risk appears to follow a time-response model consistent with a multiplicative relationship with the underlying incidence in the population—that is, risk after exposure is proportional to the background incidence of cancer over time.[27,41] Data are inconsistent as to whether the risk remains elevated throughout life. Studies in the atomic bomb survivors[31] and in women treated for benign gynecologic disorders[41,49] have shown that the excess relative risk per Gray (Gy) tends to be fairly stable over time for at least 30 years after radiation. However, the last update of the mortality experience of ankylosing spondylitis patients showed that, 25 years after irradiation, risk had decreased for a number of malignancies.[40] In the few studies of second cancer risk in which the time course beyond 20 years from first treatment was evaluated, the relative risks of solid tumor development tended to decrease in very long-term survivors.[50,51] The most recent cancer incidence report on the Japanese atomic bomb survivors, with 42 years of follow-up, indicated that the excess relative risk decreased with time for the younger age-at-exposure groups and remained virtually constant for the older cohorts.[31] Cancer incidence data from the atomic bomb survivors and five other groups exposed to radiation have been analyzed to specifically address the evolution of risk with increasing time since exposure in childhood.[52] Ten to 15 years after radiation exposure, the relative risk of solid tumors decreased with increasing follow-up time (5.7% to 6.1% per year). The excess absolute risk, however, significantly increased with time since exposure.[52]

An important part of our knowledge of radiation carcinogenesis derives from populations exposed to relatively low levels of radiation, such as the atomic bomb survivors. For solid tumors, convincing evidence for a strongly linear radiation dose-response in the lower dose ranges (up to approximately 5 Gy) has emerged.[31,35,40] The results for leukemia are less consistent, but data from most studies are compatible with a linear trend for doses of less than 1.5 to 2.0 Gy.[16,30,45] Extrapolation of radiation effects from low doses to the high-dose ranges used therapeutically cannot be done with certainty, because of the possibility of cell killing at high doses. Therefore, more recent studies of second cancer risk have focused on the shape of the radiation dose-response curve in the high-dose range.

Radiation-related leukemia risk depends on a number of parameters, such as radiation dose to the active bone marrow, dose rate, and percentage of marrow exposed. Consistent evidence indicates that the excess risk of leukemia per unit radiation dose is much higher at low doses than at the high doses administered for the treatment of malignant disease.[16,30,45,47] This phenomenon has been attributed to cell killing or inactivation of potentially leukemic cells at the higher radiation doses.[16,27] Many studies in cancer patients have shown that high radiation doses to a limited field confer very little or no increased risk of leukemia.[8,17,18,20] Both in the atomic bomb survivors and in patients who received radiotherapy for cervical cancer, leukemia risk appeared to increase with increasing average dose to the bone marrow until approximately 4 Gy, above which leukemia risk was progressively reduced with increasing dose.[16,30] However, leukemia risk in survivors of uterine cancer showed little evidence for a downturn in risk at bone marrow doses as high as 6 to 14 Gy[45]; at more than 1.5 Gy, the dose-response pattern was more or less flat, and the risk after continuous exposures from brachytherapy at comparatively low doses was similar to that after fractionated exposures at much higher doses from external beam radiotherapy. Clearly, more research is needed into the effects of dose fractionation and portion of bone marrow irradiated. Age at exposure to irradiation does not appear to greatly influence the risk of radiation-induced leukemia,[30,41,45,53] although decreasing relative risk with increasing age at exposure has been reported for one radiogenic leukemia subtype [acute lymphocytic leukemia (ALL)].[47]

In contrast, studies of radiogenic breast cancer have demonstrated that age at exposure is a major determinant of risk, with the greatest risk for those irradiated as children and adolescents.[32,50,54] Irradiation may thus affect cells of the mammary ducts before full organ development begins. Atomic bomb survivors who were younger than 10 years old at the time of the bombing had an excess relative risk per Gy five times that of women who were older than 40 years when exposed. A strong trend of increasing breast cancer risk with decreasing age at exposure was also observed in patients irradiated for Hodgkin's disease,[13,39,50,55] with no excess breast cancer risk apparent among women irradiated at 40 years or older.[13,22,35,39,55] In two studies, increased breast cancer risk after radiation exposure in childhood emerged at an early age (younger than 40), before the peak incidence in the population.[50,56] In the low-dose range, breast cancer risk increases linearly with radiation dose.[35,36,44] For a specified dose, the age-specific excess rates of breast cancer were found to be remarkably similar across studies in the Japanese atomic bomb survivors and in medically irradiated populations in the United States.[32,35] Very few studies have examined whether linear dose-response extends to the higher dose ranges used therapeutically. However, long-term survivors of Hodgkin's disease who were younger than 20 years when they received breast doses between 4 and 45 Gy from mantle field irradiation were reported to have a 40- to 75-fold increased risk of breast cancer.[13,39,57] One study found that a higher radiation dose to the mantle region (20 Gy or more vs. less than 20 Gy) was associated with a significantly greater increase of breast cancer risk.[57]

Risk of lung cancer also rises with increasing radiation dose in the lower dose range,[31,40] but studies in survivors of Hodgkin's disease[38] and breast cancer[58] suggest that the risk may level off at doses higher than 9 to 10 Gy. A similar leveling of risk at doses of 10 Gy or more has been observed for radiation-induced thyroid cancer.[59,60] However, even at thyroid doses up to 60 Gy, the risk of thyroid cancer did not decrease.[60] For bone sarcoma, two studies in survivors of childhood cancer[19,61] show no evidence of increased risk for doses less than 10 Gy to the site of the bone tumor. Beyond 10 Gy, risk for bone sarcoma rose sharply with increasing dose, reaching more than 90-fold at doses of 30 to 50 Gy.[61] Importantly, studies have shown that, also for solid tumors other than breast cancer, the excess relative risk due to radiation is much greater for children and adolescents than for adults.[12,31,50,59,62,63] Significantly greater relative risks with younger age at radiation exposure have been reported for lung cancer,[63] thyroid cancer,[31] bone sarcoma,[12,62] and gastrointestinal cancer.[50,63] After radiation in childhood, the excess relative risk per Gy for thyroid cancer [RR, 7.7; 95% confidence interval (CI), 2.1 to 28.7] is higher than for any other solid malignancy.[31]

For radiogenic lung cancer, the interaction of radiation with other risk factors, such as smoking, has been examined. Studies in uranium and tin miners exposed to radon have indicated that smoking and radiation may act multiplicatively (or at least supraadditively) in the causation of lung cancer,[64–66] implying that the absolute risk of developing radon-induced cancer is much higher in smokers than in nonsmokers. In Hodgkin's disease patients, the combined effects of smoking and high-dose radiotherapy for Hodgkin's disease were significantly stronger than multiplicative.[38,67] In the latter study, the increase in lung cancer risk with increasing radiation dose was significantly greater among patients who continued to smoke after diagnosis of Hodgkin's disease than among those who refrained from smoking. As discussed more extensively in the previous edition of this text,[68] interaction models accounting for the sequencing of radiation and smoking suggest that radiation may act as a powerful promoter of cells initiated by smoking.

The carcinogenic effects of therapeutic irradiation deserve much more study. Issues to be clarified include the shape of the radiation dose-response curve in the higher dose range, the duration of radiation-induced cancer risk and, importantly, the interaction of radiotherapy with environmental carcinogens (e.g., smoking) and genetic susceptibility. Increasing evidence suggests that genetic factors contribute to the development of radiation-induced cancers. This is perhaps best demonstrated in survivors of hereditary retinoblastoma who harbor a heterozygous germline mutation in the RB1 tumor suppressor gene, and who have a much greater risk of developing osteosarcomas within the radiation field than children irradiated for nonhereditary retinoblastoma.[69] In addition, two studies showed that patients with a positive family history of cancer are more likely to develop radiation-associated second malignancies.[70,71] In view of the postulated radiation sensitivity of heterozygous carriers of the mutated ataxia-telangiectasia (ATM) gene, it has been speculated that AT heterozygotes (approximately 1.0% of the population) may have an increased risk of radiation-induced cancer, specifically breast cancer.[72,73] In two studies, however, no ATM mutations were found in a total of 56 women who had developed breast cancer after radiotherapy for Hodgkin's disease.[71,74] Further studies should focus on the identification of other genes that may influence susceptibility to the DNA damaging effects of radiation. Such research will provide more insight into the mechanisms underlying radiation carcinogenesis and will also be of clinical benefit in minimizing radiation exposure to the most susceptible subgroups of the population.

CHEMOTHERAPY

The development of acute myeloid leukemia (AML) after chemotherapy for malignant disease was reported as early as 1970 by Kyle et al.[75] In the following three decades, the occurrence of this late effect has increased to the extent that, in some institutions, treatment-related AML now comprises up to 10% to 20% of all such entities.[76] Moreover, it is now established that the spectrum of treatment-related leukemia extends beyond AML. ALL, for example, is increasingly recognized as therapy-related[77,78] and may comprise 5% to 10% of all secondary acute leukemias.[78] Chronic granulocytic leukemia accounts for a small percentage of secondary leukemia,[77,79] and has been included in numerous analytic studies in which associations with prior chemotherapy have been evaluated,[8,17,18,20,80,81] although separate risk estimates have not been presented. To date, only chronic lymphocytic leukemia has not been convincingly associated with prior exposure to chemotherapy.

Chemotherapy is far more potent than radiotherapy in inducing leukemia. It has become evident that at least two major syndromes of treatment-related leukemia may exist[82,83]: "classic" alkylating agent–induced AML and acute leukemia related to the topoisomerase II inhibitors. Risk of alkylating agent–related leukemia typically begins to increase 1 to 2 years after the start of chemotherapy, peaks in the 5- to 10-year follow-up period, and decreases afterward.[8,13,17,20,84] Even in large patient series, the number of long-term survivors has typically been too small to determine whether 15 to 20 years after chemotherapy the risk of leukemia returns to the background level of the population.[13] Although one registry-based study indicates that leukemia risk might persist among 15-year survivors of testicular cancer,[85] it is not clear whether these late excesses might reflect the influence of salvage therapy. More than 50% of leukemias after alkylating agent therapy present initially as myelodysplastic syndromes (MDS), whereas *de novo* AML is preceded by MDS much less frequently.[77] Most cases of MDS progress to AML within 1 year.[77] Cytogenetic studies of alkylating agent–related AML/MDS have shown unbalanced chromosome aberrations, typically with loss of whole chromosomes 5 or 7 (or both), or various parts of the long arms of these chromosomes.[86] Morphologically, alkylating agent–related AML most commonly consists of French-American-British (FAB) subtypes M1/M2, but most subtypes,[77] including erythroleukemia,[20] have been observed. Survival after secondary AML is generally quite poor, typically only several months.[87]

Alkylating agents with known leukemogenic effects in humans include mechlorethamine, chlorambucil, cyclophosphamide, melphalan, semustine, lomustine, carmustine, prednimustine, busulfan, and dihydroxybusulfan.[20,77,82,88–90] Controversial findings have been reported with regard to procarbazine,[89,91] which demonstrates an underlying mechanism of action similar to alkylating agents. Few studies have addressed the relative leukemogenicity of the various alkylating drugs, but a strong body of evidence to date suggests that, at doses of equal therapeutic effect, cyclophosphamide is substantially less leukemogenic than melphalan, mechlorethamine, chlorambucil, lomustine, and thiotepa.[8,17,20,89,90,92] The risk of alkylating agent–related AML has been shown to increase with increasing cumulative dose or duration of therapy.[20,89,90] Few studies have attempted to separate the effects of cumulative dose, duration of treatment, and dose intensity, which tend to be highly correlated, but limited evidence to date suggests that cumulative dose may be a pivotal determinant of risk[20,89] (discussed later in Hodgkin's Disease).

The platinating agents cisplatin and carboplatin are among the most important cytotoxic drugs introduced since the 1960s and are widely used to treat many cancers. The platinum compounds, however, demonstrate carcinogenicity *in vitro* and in laboratory animals,[10] forming intrastrand and interstrand DNA cross-links similar to bifunctional alkylating agents. In a population-based study of women with ovarian cancer,[81] cisplatin-based combination chemotherapy was linked to significantly increased risks of leukemia (P trend for cumulative dose <.001) in a multivariate model adjusted for other treatment parameters (discussed later in Ovarian Cancer). Future studies should evaluate whether other drug combinations that include platinum might also be linked to elevated risks of leukemia, because it is not clear whether cisplatin acts as a human leukemogen only in combination with selected cytotoxic agents.

The topoisomerase II inhibitors, especially the epipodophyllotoxins, have been implicated in the development of a clinically and cytogenetically distinct type of AML. The International Agency for Research on Cancer (IARC) has concluded that the epipodophyllotoxins etoposide and teniposide are probably carcinogenic to humans.[93] Ratain and coworkers[94] were the first to recognize the potentially leukemogenic properties of etoposide-containing regimens in patients with non–small cell lung cancer, which also has been documented for patients with other types of malignancies.[95–97] As compared with "classic" alkylating agent–induced AML, epipodophyllotoxin-related AML has a shorter induction period (median, 2 to 3 years) and generally lacks a preceding phase of MDS. Furthermore, this type of AML appears to be characterized by balanced translocations involving chromosome bands 11q23, 21q22, and 3q23,[93,98] as well as morphologic features consistent with acute monoblastic or myelomonocytic leukemia (M4 or M5 according to the FAB criteria).[82,99,100] It is unclear whether epipodophyllotoxin-related AML has a better prognosis than "classic" alkylating agent–related AML, which is notoriously resistant to antileukemic treatment.[86,97]

Evidence has accumulated that the anthracyclines doxorubicin and 4-epi-doxorubicin, which are intercalating topoisomerase II inhibitors, may induce a similar type of AML as the one related to epipodophyllotoxin treatment.[17,101,102] In 1987, the IARC concluded that doxorubicin was probably carcinogenic to humans, based on a review of limited data.[88] As with many cytotoxic drugs, an evaluation of the carcinogenic potential of doxorubicin is complicated, because it is typically given in combination with other chemotherapeutic agents, including alkylators.[17,101–103] Curtis et al.[20] found no increase in the risk of leukemia associated with doxorubicin therapy for breast cancer, after adjusting for the effects of alkylating agents and radiotherapy. Although increasing dose of doxorubicin to treat childhood cancer seemed weakly associated with an increased risk of leukemia after adjustment for alkylating agents,[18] the investigators concluded that the excess risk was almost completely attributable to alkylators. In a study of children with Wilms' tumor,[104] the relative risk of leukemia (six cases) after doxorubicin-containing regimens was approximately 14-fold; however, because a relatively constant dose (300 mg/m^2) of doxorubicin was used and data for treatment of relapse were incomplete, evaluation of a dose-response relation was not possible.

The relative leukemogenicity of the anthracyclines and different epipodophyllotoxins is not known. Furthermore, it is unclear whether the schedule of administration or the cumulative dose is the major determinant of leukemia risk (discussed in more detail later in the sections Testicular Cancer and Pediatric Malignancies).[95–97,105,106] In view of the widespread use of epipodophyllotoxins and anthracyclines in curative treatments, continued evaluation of the leukemogenic potential of these agents is urgently needed.[83,106] Detailed descriptions of molecular mechanisms involved in the development of AML after administration of these cytotoxic drugs have been provided elsewhere.[82,83,107–109] As postulated by Pedersen-Bjergaard and Rowley,[82] cytostatic drugs with different mechanisms of action [i.e., direct binding to DNA (alkylating agents) and inhibition of DNA-topoisomerase II (epipodophyllotoxins and anthracyclines)] may have a synergistic effect in leukemogenesis.

The antimetabolites have generally not been regarded as carcinogenic,[88] and Cheson et al.[110] observed that nucleoside analogue therapy for chronic lymphocytic leukemia did not appear to confer a significantly increased risk of second cancer. However, in a report[111] from St. Jude's Children's Research Hospital, it was shown that children with ALL who received cranial irradiation and who had wild-type thiopurine methyltransferase phenotype had an 8.3% cumulative risk of brain cancer, while children with ALL who received irradiation and had a defective phenotype had a 42% risk (P = .0077). Patients also had received concurrent systemic chemotherapy with high-dose (75 mg/m^2) 6-mercaptopurine plus high-dose methotrexate. It was hypothesized that the defective thiopurine methyltransferase activity resulted in higher exposures to thioguanine nucleotide metabolites of 6-mercaptopurine during the period of radiation.

Just as the pharmacology of effective cancer chemotherapy is impacted by underlying principles of pharmacokinetics and pharmacodynamics (see Chapter 19.1), these influences likely contribute to the development of secondary leukemia. The possible role of polymorphisms in drug-metabolizing genes, including the cytochrome P-450 enzymes, glutathione S-transferases, and arylamine

N-acetyltransferases in chemotherapy-related leukemias has been reviewed.[112] Felix et al.[113] described an association between CYP3A4 genotype and treatment-related leukemia. Other factors in the development of chemotherapy-related leukemias may include interindividual differences in repair of DNA damage,[114,115] germline mutations in tumor suppressor genes,[76,112] administration of concomitant medications, and interpatient variation in renal and hepatic function. Clarification of the important interrelationships between these factors are critical to a better understanding of individual susceptibility to secondary leukemia. Because cancer patients frequently receive large doses of cytotoxic drugs, interindividual differences in drug absorption, distribution, metabolism, and excretion are accentuated. Until these influences and their interrelationships are better understood, empiric end points, such as the development of acute hematopoietic toxicity after chemotherapy, might be explored for their value as possible surrogate markers of secondary leukemia risk.[89] For cytotoxic agents for which both oral and intravenous formulations are available, the route of administration in describing dose-response associations with secondary leukemia risk should also be taken into account.[81] Whether chemoprotectants such as amifostine (WR-2721), which ameliorates the myelosuppressive effects of alkylating agents[116] and platinum compounds,[117] might possibly contribute to decreased risks of second leukemias should be examined.

Many chemotherapeutic agents are known mutagens and animal carcinogens,[88] and the induction period of solid tumors may be longer than the observation period available in published research. Thus, the question of whether the increased risks of leukemia after chemotherapy might be later followed by excess solid tumors is important. To date, the causal link between cyclophosphamide and bladder cancer represents one of the few established relationships between a specific cytostatic drug and a solid tumor (reviewed later in Non-Hodgkin's Lymphoma).[21,118,119] Elevated risks of bone sarcomas[19,61] and possibly lung cancers[120,121] also have been observed after alkylating agent chemotherapy. The contribution of chemotherapy to radiation-induced solid tumors[50,55,104,111,122] should also be investigated. For example, as discussed in the section Pediatric Malignancies, doxorubicin has been found to potentiate the development of second solid tumors after radiation for Wilms' tumor.[104] The investigators of this study[104] hypothesized that doxorubicin may inhibit the repair of radiation-induced damage, likely through its interaction with DNA topoisomerase II. Newton et al.[123] reported a significantly shorter time to bone sarcoma in children given both anthracyclines and radiation to treat cancer. The radiation enhancement properties of other cytotoxic drugs (e.g., platinum, hydroxyurea, and 5-fluorouracil) have been well described[124]; whether these features might be correlated with increased risk of solid tumors in cancer patients who survive long term after radiotherapy might also be explored.

RISK OF SECOND MALIGNANCY IN PATIENTS WITH SELECTED PRIMARY CANCERS

HODGKIN'S DISEASE

In view of the excellent cure rates that are currently achieved in the relatively young population of Hodgkin's disease patients, it has become increasingly important to evaluate how the occurrence of second cancers affects their long-term survival. Since the first reports of increased second cancer risk in Hodgkin's disease patients in the early 1970s,[125,126] nearly all major treatment centers have evaluated second cancer risk in their patients. An excess of AML in chemotherapy-treated patients and an increased risk of solid tumors in radiotherapy-treated patients have been reported consistently in the literature.[127] The overall risk of selected second malignancies compared with the general population is given in Table 55.7-1, based on a combined analysis of three studies that included a total of 9618 patients.[50,63,128]

The largest relative risk (95-fold) is observed for AML, followed by a 19-fold increased risk for NHL, tenfold excesses for connective tissue and bone cancers, and a ninefold elevated risk for thyroid cancer. Moderately increased risks (two- to fivefold) are observed for a number of solid tumors, such as cancers of the lung, stomach, colon, breast, mouth, and pharynx, as well as melanoma. Because AML and NHL are diseases with a low incidence in the general population, even a high relative risk compared to the population may translate into a low cumulative (actuarial) risk. As shown in Figure 55.7-1, for the entire follow-up period, the cumulative risk of solid tumors far exceeds that of leukemia or NHL.[50] Absolute excess risk is the best measure to judge which subsequent tumors contribute most to the second cancer burden. Table 55.7-1 shows that, compared with the general population, Hodgkin's disease patients experience an excess of 62 malignancies per 10,000 person-years of observation. Solid tumors account for the majority of excess cancers (38 per 10,000 patients per year), with lung cancer contributing 13 excess cases per 10,000 person-years. Leukemia and NHL each account for approximately 12 cases per 10,000 person-years.

The evolution of second malignancy risk over follow-up time varies by tumor site. In the majority of studies, increased leukemia risk is observed as early as 2 to 4 years after initiation of chemotherapy, with peak occurrence between 5 and 9 years and decreasing risks thereafter.[8,13,48,50,57,63] In studies with large numbers of long-term survivors, significantly increased relative risks are still observed for 15 years after first treatment.[13,50,63] The relative risk of NHL is already greatly increased in the first 5 years after treatment. In some studies, the risk remains rather constant over time,[48,55] whereas others report that risk increases with time since treatment.[12,13] The relative risk of solid tumors is minimally elevated in the 1- to 4-year follow-up period and increases steadily with increasing follow-up time from 5 years since first treatment.[12,13,48,50,55,63,84] For several tumor sites (breast, thyroid), the excess risk does not become apparent until after 10 or even 15 years of observation. In the few studies that include data on 20-year survivors, the relative risk of solid tumors continued to increase through the 15- to 20-year follow-up period.[13,39,50,55,57,63,84,122] Almost no data are available on the time course of risk 20 or more years after treatment. In a study of patients diagnosed with Hodgkin's disease before age 40 in the Netherlands, the relative risk of solid tumor development in 25-year survivors was somewhat lower than in the 15- to 24-year follow-up period (RRs of 5.3 and 8.8, respectively; $P = .29$), suggesting that relative risk may decrease in very long-term survivors.[50] In this study, the 25-year risk of developing any second malignancy was 27.7% (95% CI, 23.1% to 32.8%), compared with 4% in the general population (see Fig. 55.7-1).[50] Because the relative risks of leukemia, NHL, and solid tumors each show a distinctive pattern with

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TABLE 55.7-1. Relative Risk of Second Cancers after Hodgkin's Disease: Combined Results from Three Large Studies in 9618 Patients

Site or Type	*Observed Cases*	*Expected Cases*	*Relative Risk (O/E Cases)*	*95% Confidence Interval*	*Absolute Excess Risk per 10,000 Patients per Year*
All cancers	747	195.0	3.8	3.6–4.1	62.2
Leukemia	116	5.2	22.3	18.4–26.7	12.5
Acute nonlymphocytic leukemia[a]	63	0.7	94.8	72.9–121	14.9
Non-Hodgkin's lymphoma	112	6.0	18.5	15.2–22.3	12.0
Solid tumors	519	183.8	2.8	2.6–3.1	37.9
Lung	155	36.1	4.3	3.6–5.0	13.4
Mouth and pharynx	18	4.8	3.7	2.2–5.9	1.5
Stomach	29	10.4	2.8	1.9–4.0	2.1
Colon	46	24.3	1.9	1.4–2.5	2.4
Bone	7	0.7	10.1	4.0–20.8	0.7
Connective tissue	15	1.5	9.8	5.5–16.2	1.6
Melanoma	21	5.1	4.1	2.5–6.3	1.8
Female breast	76	28.5	2.7	2.1–3.3	13.2
Bladder	10	9.3	1.1	0.5–2.0	0.1
Thyroid	14	1.5	9.2	5.0–15.4	1.4
Pancreas	8	4.8	1.7	0.7–3.3	0.4
Liver	6	0.9	6.5	2.4–14.2	0.7
Cervix	11	4.3	2.6	1.3–4.6	2.5
Prostate	8	7.3	1.1	0.5–2.1	0.2
All solid tumors except lung cancer	364	147.7	2.5	2.2–2.7	24.4
Gastrointestinal tract	115	48.6	2.4	2.0–2.8	7.0

O/E, observed/expected.
[a]Reported only in refs. 50 and 128.
(Based on results from refs. 50, 63, and 128.)

time since first treatment, the absolute excess risks in 10-year survivors differ greatly from those observed in the entire patient population. Based on combined estimates from two of the studies included in Table 55.7-1,[50,63] lung cancer contributes most to the absolute excess risk in 10-year survivors, with 22 excess cases per 10,000 patients per year, followed by NHL (16 per 10,000 per year), gastrointestinal tract tumors (15 per 10,000 per year), and leukemia (7 per 10,000 per year). In females, breast cancer accounts for most of the absolute excess risk in 10-year survivors (58 per 10,000 per year).[39,50]

For several second malignancies, the association with treatment factors has been investigated in detail. Leukemia after Hodgkin's disease is certainly the most studied malignancy

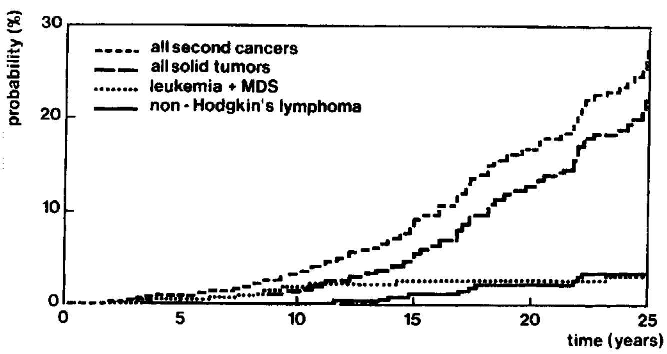

FIGURE 55.7-1. Cumulative risk of second cancers in 1253 patients with Hodgkin's disease diagnosed younger than 40 years of age. MDS, myelodysplastic syndromes. (From ref. 50, with permission.)

induced by treatment, and extensive knowledge of its risk factors has emerged.[127] Radiotherapy alone is associated with very little or no increased risk of leukemia,[12,48,63,84,89] whereas alkylating agent chemotherapy is linked with greatly elevated risk. Several studies have compared the leukemogenicity of different chemotherapy regimens. Risk of AML rises sharply with an increasing number of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP or MOPP-like) cycles.[8,89] The risk associated with 10 to 12 MOPP cycles appears to be approximately three to five times higher than the risk after six MOPP cycles.[8,89] Since the 1980s, MOPP-only chemotherapy has been gradually replaced by doxorubicin, bleomycin, vinblastine, and dacarbazine [ABV(D)]-containing regimens in many centers. Only a few reports have described AML occurrence after ABV(D) alone. Patients treated with ABVD in the Milan Cancer Institute, where this regimen was designed, were shown to have a significantly lower risk of AML than MOPP-treated patients (15-year cumulative risks of 0.7% and 9.5%, respectively).[129] Another study showed that Hodgkin's disease patients treated with MOPP/ABV(D)-containing regimens in the 1980s had a substantially lower risk of AML/MDS than patients treated in the 1970s with MOPP alone (10-year cumulative risks of 2.1% and 6.4%, respectively, $P = .07$).[13] The German-Austrian Pediatric Hodgkin's Disease Group observed a low risk of AML (1.1% at 15 years) after regimens that contained relatively low doses of procarbazine, doxorubicin, and cyclophosphamide, without mechlorethamine.[130]

An important question is whether radiotherapy adds to the leukemia risk associated with chemotherapy. Evidence that combined modality treatment results in greater risk than chemotherapy alone is provided by several reports,[84,129,131] whereas other large series indicate that the risk of AML after combined treatment is comparable to that after chemotherapy alone.[8,12,13,48,57,63,89,91] These inconsistent results may be due partly to differences in treatment regimens between studies but also to lack of adjustment for type and amount of chemotherapy in some reports. The interaction between radiotherapy and chemotherapy could be evaluated most rigorously in the large case-control study by Kaldor and associates,[8] which included 163 cases of leukemia after Hodgkin's disease. When examining the combined effects of radiation dose to the active bone marrow and number of mechlorethamine-procarbazine containing cycles, it was found that, for each category of radiation dose (less than 10, 10 to 20, and more than 20 Gy to the marrow), leukemia risk clearly increased with the number of chemotherapy cycles. In contrast, among patients with a given number of chemotherapy cycles, risk of leukemia did not consistently increase with higher radiation dose. Taken together, the preponderance of available data does not support the hypothesis that the combination of chemotherapy and radiotherapy confers a higher risk of leukemia than chemotherapy alone.

Several studies have identified splenectomy as an independent risk factor for the development of AML,[8,84,91,129,132] with an approximate twofold difference in risk between patients who did and did not undergo a splenectomy. In other reports, however, splenectomy was either not linked or was only weakly related to leukemia risk.[57,131] The mechanism underlying the association with splenectomy remains unclear, but a relationship with immunologic function of the spleen seems likely.[89]

The modifying effect of host-related factors, such as age, on leukemia risk in Hodgkin's disease survivors has been examined in a number of studies and has been reviewed elsewhere.[127] The reported higher *cumulative* risk of AML in older Hodgkin's disease patients as compared to younger ones simply reflects the higher baseline incidence of the disease in older persons. In the few studies that have analyzed *relative* risk of leukemia by age, based on comparisons to general population expectations, no differences between age groups were observed,[12,50,55] or the relative risk of AML was even significantly greater at younger ages than at older ages.[8,63] The risk of AML in relation to treatment-associated acute and chronic bone marrow toxicity has been examined in only one study to date.[89] Significantly increased risks of leukemia were found among patients who developed thrombocytopenia, either in response to initial therapy or during follow-up. After adjustment for type and amount of chemotherapy, patients who showed a decrease of 70% or more in platelet counts after initial treatment had an approximately fivefold higher risk of developing leukemia than patients who showed a decrease of 50% or less. Severe acute thrombocytopenia may indicate greater bioavailability of cytotoxic drugs, which would likely contribute to the development of leukemia.

Although increased risks of NHL after Hodgkin's disease are consistently reported, the causes of the excess risk are not well understood.[127] Because increased risks of NHL occur in immunosuppressed patients, such as transplantation recipients,[133] and because Hodgkin's disease may be accompanied by immunosuppression,[134] several investigators have argued that the elevated risk of NHL may be attributed to Hodgkin's disease itself rather than to its treatment. This view is supported by several studies in which risk did not vary appreciably between treatments.[12,48,55,63] In other studies, however, the risk of NHL was found to be lowest among patients treated with radiotherapy alone and highest among patients who received intensive combined modality treatment, both initially and for relapse.[13,84,135,136] The inconsistent results regarding the relationship with treatment may be partly attributed to diagnostic misclassification—that is, misdiagnosis of the primary tumor as Hodgkin's disease, whereas NHL was represented according to modern lymphoma classification schemes.[127] In only very few studies were diagnostic pathology slides of the second NHL and original Hodgkin's disease reviewed to avoid such misclassification.[13,48] Although transformation to NHL may be part of the natural history of some types of Hodgkin's disease, the role of intensive combined modality treatment and its associated immunosuppression should be explored further.

Increased risks of solid cancers after Hodgkin's disease generally have been attributed to radiotherapy.[12,13,39,48,50,55,57,84,122,127,137] Excesses of melanoma, however, are more likely to be related to immunosuppression accompanying Hodgkin's disease or its treatment, because elevated risks appear as early as in the 1- to 4-year follow-up interval.[63,138] The other sites for which excess solid cancers have been reported (lung, breast, gastrointestinal tract, thyroid, bone, connective tissue) are those for which elevated risks also have been described in other radiation-exposed cohorts.[26,28] One case-control study examined lung cancer risk in relation to the radiation dose to the affected lung area, as well as the modifying effect of the patient's smoking habits.[38] Based on 30 cases of lung cancer in a cohort of 1939 patients with Hodgkin's disease, it was observed that lung cancer risk rose with increasing radiation dose (P trend = .01), with a relative risk of 9.6 (95% CI, 0.93 to 98.0) for patients who received 9 Gy or more as compared to those who received less than 1 Gy. The increase in risk of lung cancer with increasing radiation dose was significantly greater among patients who smoked after diagnosis of Hodgkin's disease than among those who refrained from smoking.

A very important question is whether chemotherapy for Hodgkin's disease can also induce solid cancers, and if so, at which sites. A few studies have raised concern about a possible long-term effect of chemotherapy on lung cancer risk.[48,63,120] The British National Lymphoma Investigation cohort study of 2846 patients[48] showed a significantly increased risk of lung cancer after chemotherapy alone, with the relative risk (4.2; 95% CI, 2.2 to 7.3) of similar magnitude as that observed in patients treated with either extensive radiotherapy or combined modality treatment. A similar excess risk of lung cancer in patients given chemotherapy, but no radiotherapy, was found in a more recent expansion and update of this study.[63] No increased risk of lung cancer, or solid tumors overall, followed chemotherapy alone in several other series.[12,50,57,84,89] However, the expected number of solid tumors 10 or more years after chemotherapy alone was less than two in nearly all negative studies, rendering it impossible to exclude a moderate increase in risk. If chemotherapy indeed affects solid tumor risk, one would expect that patients receiving combined modality treatment would have a greater relative risk than patients treated solely with radiotherapy. Only one study to date has reported a significantly greater risk for solid cancers overall after chemotherapy and radiotherapy compared with irradiation alone,[55] whereas no such difference has been found in the majority of investigations.[12,48,57,84,89,128] However, for selected solid cancer sites (e.g., gastrointestinal tract), larger risks were observed after combined modality treatment than after irradiation alone.[50,63,122] For lung cancer risk in irradiated patients, two case-control studies showed no association with chemotherapy overall, the number of cycles, or the cumulative doses of mechlorethamine and procarbazine,[38,120] which argues against an important contribution of chemotherapy to lung cancer risk.

The inconsistent results reported with regard to the influence of chemotherapy on solid tumor risk may be partly related to the fact that most studies considered all solid tumors combined, whereas chemotherapy may differentially affect the risk of tumors at disparate sites. A study from the Netherlands Cancer Institute demonstrated that the addition of salvage chemotherapy to initial radiotherapy, as compared to initial irradiation alone, did not influence the risk of solid cancers overall but significantly increased the risk of solid tumors other than breast cancer (RR, 9.4, compared to 4.7 for initial irradiation alone).[50] Conversely, patients who received salvage chemotherapy were found to experience significantly lower risks of breast cancer than patients treated with radiotherapy alone (RRs of 2.8 and 7.6, respectively), possibly related to premature ovarian failure due to intensive chemotherapy.[50] Additional studies are warranted to examine which cytotoxic drugs might be responsible for site-specific increased risks of solid tumors.

The strongly elevated risk of breast cancer after radiotherapy for Hodgkin's disease has become a major concern for female survivors.[139–141] In a Dutch study, 27 cases of breast cancer were observed in 544 female patients diagnosed with Hodgkin's disease during adolescence or young adulthood and were followed for an average of 14 years.[50] Women with follow-up equal to or exceeding 15 years had 9.4-fold increased risk of breast cancer as compared with the general population. The risk of developing breast cancer increased dramatically with younger age at first irradiation. Fifteen-year survivors who had radiation treatment before 20 years of age had an 18-fold increased risk of breast cancer; women irradiated at ages 20 to 29 had a sixfold increased risk; and a small, nonsignificant increase was observed for women irradiated at age 30 or older (RR, 1.7). A similar trend, with even larger relative risks, has been reported from Stanford University.[39] An approximately 100-fold increase of breast cancer risk has been observed after treatment at younger than 16 years of age, with relative risks ranging from 17 to 458.[39,55,57,142] This huge variation in estimated risk is not surprising in view of the large differences between series in important variables such as proportion of patients irradiated, duration of follow-up, and completeness of follow-up. Generally, surveys with more complete follow-up have found lower relative risks of breast cancer[50,63,142,143] than those in which completeness of follow-up was less satisfactory or not addressed.[55,57,144] Incomplete follow-up may lead to overestimation of second malignancy risk if patients who remain well lose contact with clinical follow-up, whereas those with second cancer come to attention because of this. The very high *actuarial* risks reported in two U.S. studies (34% at 25 years after first treatment for women treated at younger than 20 years of age,[144] and 35% at 40 years of age for those treated when younger than 16 years[57]) are likely to be exaggerated estimates, not only because of losses to follow-up, but also because the actuarial method is less appropriate when including events that occur at follow-up intervals later than those at which data for most of the patients were censored.[139] In the more recently published Dutch study, with (nearly) complete follow-up, the 25-year actuarial risk of breast cancer amounted to 16%, both for women first treated before the age of 20 and at ages 20 to 30.[50] In two studies, the majority of breast cancers arose within or at the margin of the anterior radiation field, in breast tissue that had received a treatment dose of 40 to 46 Gy.[39,57] Because it is not known whether breast cancer risk is linearly related to radiation dose in the therapeutic dose range, it will be of interest to see whether the reduced mantle field doses in current treatment protocols will result in lower breast cancer risk.

Several studies have demonstrated that age at treatment for Hodgkin's disease is also a crucial determinant of increased relative risks for solid malignancies other than breast cancer.[50,63,122] Van Leeuwen and colleagues[50] reported that the relative risks of nonbreast solid tumors were 4.9, 6.9, and 12.7 for patients first treated at ages 31 to 39, 21 to 30, and 20 or younger, respectively (Table 55.7-2). Data from Stanford University and the United Kingdom show that the highest relative risks for gastrointestinal cancers (approximately eightfold)[63,122] and thyroid cancer[63] occur among patients treated before age 25, with no excesses observed for those treated after 45 years of age. Importantly, Table 55.7-2 demonstrates that the *absolute excess risk* of developing a solid cancer does not show much variation by age at first treatment, probably because the increasing background incidence of solid tumors with age in the population at large outweighs the stronger increase of *relative* risk at younger ages.

The strongly increased relative risks of solid tumors in patients treated for Hodgkin's disease at a young age only become manifest after an extended follow-up period. This might point to a prolonged induction period, but it may also be due to this young patient group reaching an age at which solid tumor incidence begins to rise in the general population. Although a few studies addressed the relative risk of solid malignancies according to attained age,[39,50,122] only one study distinguished the separate contributions of age at first treatment and attained age.[50] Solid tumor risk was greatest among patients treated at a young age (20 years or younger), but the largest relative risk emerged *before* the patients attained the age range at which solid tumors normally occur. Among patients first treated at age 20 or before, the relative risk of developing a solid tumor at ages 40 to 49 was significantly lower than the relative risk of solid tumor development before age 40 (RR, 4.2 vs. 27.9; $P = .0001$). It is notable that a similar finding has been reported with regard to breast cancer risk among atomic bomb survivors in Japan.[145]

In conclusion, the occurrence of treatment-related second cancers is a major problem in survivors of Hodgkin's disease. The substantial increase in solid tumor risk with time since Hodgkin's disease diagnosis necessitates careful, lifelong medical surveillance of all patients. The greatly increased risk of NHL throughout follow-up demonstrates the importance of performing biopsies in recurrent Hodgkin's disease. Because smokers experience a significantly greater risk of lung cancer attributable to radiotherapy than nonsmokers, physicians should make a special effort to dissuade Hodgkin's disease patients from smoking, even before treatment starts. Women treated with mantle field irradiation before age 30 are at greatly increased risk of breast cancer. The importance of regular breast examinations should be explained to them, and they should be taught to perform monthly breast self-examination. From 8 years after irradiation, the follow-up program of these women should include yearly breast palpation and mammography. Physicians should also be alert to the higher risk of gas-

TABLE 55.7-2. Relative and Absolute Excess Risks of Second Cancer in 1253 Patients with Hodgkin's Disease, According to Age at Start of Treatment

Type of Second Cancer and Age at Diagnosis of Hodgkin's Disease	*Observed Cases*	*Relative Risk*	*95% Confidence Interval*	*Absolute Excess Risk per 10,000 Patients per Year*
All malignancies				
≤20	28	13.3	8.8–19.2	58.3
21–30	61	8.2	6.3–10.5	72.2
31–39	48	4.9	3.6–6.4	86.6
Solid tumors				
≤20	25	13.9	9.0–20.6	52.3
21–30	43	6.5	4.7–8.8	49.1
31–39	38	4.2	3.0–5.8	65.9
Breast cancer				
≤20	9	16.9	7.8–32.2	37.8
21–30	12	5.6	2.9–9.8	29.6
31–39	6	2.4	0.9–5.2	18.9
Non-breast solid tumors				
≤20	16	12.7	7.2–20.6	33.2
21–30	31	6.9	4.7–9.8	35.8
31–39	32	4.9	3.4–7.0	57.9
Gastrointestinal cancer				
≤20	7	35.7	14.4–73.6	15.3
21–30	11	10.5	5.3–18.9	13.4
31–39	8	4.3	1.9–8.5	14.0
Non-Hodgkin's lymphoma				
≤20	1	10.3	0.3–57.6	2.0
21–30	6	19.5	7.1–42.4	7.7
31–39	9	26.4	12.1–50.2	19.7
Leukemia				
≤20	2	27.6	3.3–99.5	4.3
21–30	14	73.0	39.9–123	18.6
31–39	2	9.3	1.1–33.4	4.1

(From ref. 50, with permission.)

trointestinal cancers in patients who received paraaortic and pelvic radiation fields. Thorough examination of gastrointestinal complaints is indicated. An important question to be answered in future research is whether, in long-term survivors, chemotherapy contributes to the risk of solid tumors, and if so, which cytotoxic drugs are responsible for the excess risk. The most devastating second malignancy to occur among patients cured of Hodgkin's disease remains chemotherapy-related leukemia. Because the poor prognosis of this complication cannot be changed by early diagnosis, it is promising that leukemia risk has decreased dramatically with the introduction of ABV-based regimens in the 1980s. It is hoped that current treatment protocols that limit the dose and fields of radiotherapy will similarly reduce the late risk of solid cancers.

NON-HODGKIN'S LYMPHOMA

Although surveys in the past[146,147] concluded that NHL patients are not at increased risk for second solid tumors, most either predated the advent of modern therapeutic approaches or lacked sufficient statistical power to detect all but very high risks. Due largely to the introduction of effective treatment, NHL patients now demonstrate a 5-year relative survival rate of approximately 51%.[148] Commensurate with improvements in life expectancy, several large follow-up studies of NHL patients reported significantly increased risks of second cancers.[149,150] In the largest published study to date, the incidence of second malignancies was estimated in 29,153 patients diagnosed with NHL between 1973 and 1987 in one of nine population-based areas participating in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program.[149] Significantly increased risks were observed for all second cancers taken together (observed/expected [O/E] = 1.2; O = 1231), with excesses increasing with follow-up time to reach 1.8 in 10-year survivors. A subsequent international survey of 6171 2-year survivors of NHL confirmed the increased risk of second cancer and showed that significant excesses persisted for two decades.[150] In an update of the SEER program data, which included more than 48,000 patients diagnosed with NHL between 1973 and 1993, significantly increased site-specific risks were observed for cancers of lip (O/E = 2.0), lung (O/E = 1.4), kidney (O/E = 1.3), bladder (O/E = 1.4), thyroid (O/E = 2.0), and bone (O/E = 4.1), as well as AML (O/E = 3.6) (L. Travis, unpublished observations). Although registry-based treatment data are incomplete, it appeared that chemotherapy was related to subsequent AML and to bladder cancer and that

TABLE 55.7-3. Risk of Bladder Cancer According to Cumulative Dose and Duration of Cyclophosphamide Therapy

Cyclophosphamide	*Median Dose or Duration*[a]	*Cases*	*Controls*	*Matched Relative Risk*[b]	*95% Confidence Interval*
CUMULATIVE DOSE					
<20 g[c]	10.0 g	8	22	2.4	0.7–8.4
20–49 g	34.0 g	5	6	6.3[d]	1.3–29.0
≥50 g	87.7 g	5	2	14.5[d,e]	2.3–94.0
DURATION OF THERAPY					
<1 y	6 mo	8	20	2.5	0.7–9.0
1–2 y	18 mo	3	6	3.7	0.6–22.0
>2 y	51 mo	7	4	11.8[d,e]	2.3–61.0

[a]Median cumulative dose of cyclophosphamide or median duration of therapy among all patients within the specified category.
[b]The referent group consists of six case subjects and 42 control subjects who were not treated with cyclophosphamide and who received a radiation dose to the bladder of 0.5 Gy or less. The multivariate model also included terms for patients who received radiotherapy without cyclophosphamide (six case subjects and 16 control subjects).
[c]The minimum cumulative dose of cyclophosphamide in this group was 2.1 g.
[d]$P<.05$.
[e]P for trend <.005.
(From ref. 21, with permission.)

radiotherapy was associated with AML and, possibly, cancers of lung, bladder, and bone.

The excesses of second genitourinary cancers[21,118] and AML[14,90,151–155] have been examined in relationship to treatment for NHL. The largest investigation[21] of secondary bladder tumors was set within a cohort of 6171 2-year survivors of NHL and included 31 patients with transitional cell carcinoma, along with 17 cases of kidney cancer. Detailed information on chemotherapeutic drugs and cumulative dose was collected for all subjects, and radiation dose to the target organ was estimated from individual radiotherapy records. A significant 4.5-fold risk of bladder cancer followed therapy with cyclophosphamide, with risk strongly dependent on cumulative dose (Table 55.7-3).

Significantly elevated sixfold and 14.5-fold risks followed cumulative doses of 20 to 50 g and 50 g or more, respectively (P trend = .004). Neither radiotherapy nor cyclophosphamide was associated with excess kidney cancers. The absolute risk of bladder cancer predicted during 15 years of follow-up was on the order of three excess cancers per 100 NHL patients who had been given cumulative doses of between 20 and 50 g. At cumulative doses of 50 g or more, the excess risk increased to approximately seven bladder cancers per 100 NHL patients.

NHL treatment has been linked to excess risks of AML in several studies,[14,90,151–155] which have been reviewed.[155] Because leukemic progressions of NHL (lymphocytic leukemias) are relatively frequent, histopathologic confirmation of AML diagnosis has been an essential part of all series in which leukemia risk was examined. The largest investigation to date[90] included 11,386 2-year survivors of NHL, among whom 35 cases of AML or MDS were identified. The risk of AML was only weakly associated with the use of cyclophosphamide-containing regimens (RR, 1.8; 95% CI, 0.7 to 4.9) and did not increase with increasing cumulative dose or duration of treatment. However, the median cumulative dose of cyclophosphamide was only 12.5 g, which is considerably lower than in previous studies[14,152] in which nine leukemia cases each were included and substantially higher risks (RR, 105 and 76, respectively) were reported. The weak association between cyclophosphamide at lower dose levels and AML,[90] however, supports other evidence that the drug has a low leukemogenic potential.[8,20,92] Among 10,000 NHL patients treated for 6 months with chemotherapy regimens containing low cumulative doses of cyclophosphamide, an excess of four AMLs might develop in 10 years of follow-up.[90] This is an important conclusion in view of the frequent use of cyclophosphamide-containing regimens in current treatment regimens for NHL. Risk of AML after alkylating agent therapy did not vary significantly by age at NHL diagnosis or gender when evaluated by multivariate methods.

Low-dose total body irradiation (TBI), as used in past treatment approaches for NHL, seems linked with an unusually high occurrence of secondary leukemias.[155,156] This treatment modality used very low individual TBI fraction sizes (most commonly 10 to 15 cGy) given several times a week until a cumulative dose of approximately 150 cGy was administered. The risk of leukemia after low-dose TBI was quantified in a study of 61 2-year NHL survivors who received low-dose TBI as primary therapy.[155] Four patients developed AML (RR, 117 compared with population rates; 95% CI, 31.5 to 300.0). A fifth patient was diagnosed with MDS. All five patients with secondary hematologic malignancies had received salvage treatment with either alkylating agents alone or combined modality therapy. It is noteworthy that the excess risk of AML after low-dose TBI[155] was much greater than the risk observed in the larger international investigation of AML after NHL,[90] although similar chemotherapy regimens were used. Other types of NHL treatment that combine high-dose, large-field radiotherapy with alkylating agents also have been associated with very large risks (100- to 1000-fold) of AML.[14,151] It is likely that the chemotherapy contributed to the excess risk of leukemia, either directly or by

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DURATION OF THERAPY					
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[a]Median cumulative dose of cyclophosphamide or median duration of therapy among all patients within the specified category.
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[d]P<.05.
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Estimates of the cumulative risk of secondary MDS/AML 5 to 6 years after autologous bone marrow transplantation (ABMT) for NHL range from 4% to 18%.[6,158,159] Based on long-term follow-up of a large cohort, Friedberg et al.[160] reported that the actuarial risk at 10 years was approximately 20%, with no evidence of a plateau. Because most lymphoma patients tend to be intensively treated, even before ABMT,[158,159] the roles of prior therapy and the preparative regimen for transplantation in the development of leukemia are difficult to distinguish.[6,158,159] In a review, Traweek et al.[161] concluded that although the available evidence suggests that prior therapy makes a pivotal contribution to risk of secondary leukemia, an ancillary role for the transplantation procedure itself can not be excluded. The investigators[161] suggested that the incidence of leukemia after ABMT for lymphoma might be reduced by earlier transplantation or stem cell harvest (or both) and the screening of bone marrow for karyotypic abnormalities before autologous grafting. Based on analyses of pretransplant specimens, Abruzzese and colleagues[162] suggested that, in many cases of MDS after ABMT, stem cell damage results from prior chemotherapy.

In conclusion, survivors of NHL are at increased risk for a number of second malignancies, albeit much less so than patients with Hodgkin's disease. To date, the excess risks of AML and bladder cancer have been demonstrated to be treatment-related. To assess risk factors for leukemia after ABMT, there is a strong need for a large study with data on prior therapy, the transplant preparative regimen, and the transplantation procedure itself.

TESTICULAR CANCER

The introduction of cisplatin into chemotherapy protocols for testicular cancer represents one of the landmark accomplishments of modern cancer treatment.[163] Testicular cancer is now largely curable, with a 5-year relative survival rate of approximately 95%.[148] Although effective therapy for early-stage seminoma with infradiaphragmatic radiotherapy has been used for many decades, treatment with platinum-based chemotherapy for nonseminoma and advanced seminoma was not widely available until the late 1970s. In the interim period, radiotherapy fields to treat testicular cancer have decreased in size and smaller doses are used,[164] but patients treated with earlier, more aggressive approaches remain at risk for possible late sequelae. Few studies have addressed the long-term risks of second cancers among a sizable number of survivors[85,165–167] that also take into account the histologic type of testicular tumor.[85] The largest study of second malignant neoplasms after testicular cancer included 28,843 1-year survivors diagnosed with a first primary cancer of the testis between 1935 and 1993 and reported to 16 population-based cancer registries in North America and Europe.[85] More than 3300 testicular cancer patients survived more than 20 years after diagnosis. Second cancers, excluding contralateral testis, developed in 1406 patients (O/E = 1.43; 95% CI, 1.36 to 1.51) (Table 55.7-4).

The absolute risk was 16 excess cancers per 10,000 men per year. Significantly elevated risks were observed for all second solid tumors (O/E = 1.4; O = 1251), with significant site-specific excesses for ALL, acute nonlymphocytic leukemia, melanoma, NHL, and cancers of the stomach, colon, rectum, pancreas, prostate, kidney, bladder, thyroid, and connective tissue. Second cancer risk was similar after seminomas (O/E = 1.4) and nonseminomatous tumors (O/E = 1.5), with little variation in site-specific patterns. Increased risks for cancers of small intestine (O/E = 4.4) and rectum (O/E = 1.6) were observed only for seminomas, whereas patients with nonseminomatous germ cell tumors (GCT) showed elevated twofold risks for hepatobiliary cancer. Risk of solid tumors increased with time since diagnosis of testicular cancer to reach 1.5 after 20 years (*P* trend = .00002). Among 20-year survivors, 369 (O/E = 1.5) solid tumors were reported, with significant excesses for cancers of stomach (O/E = 2.3), colon (O/E = 1.7), pancreas (O/E = 3.2), prostate (O/E = 1.4), kidney (O/E = 2.3), bladder (O/E = 2.8), and connective tissue (O/E = 4.7).[85] The actuarial risks of developing any second cancer, excluding contralateral testicular tumors, were 15.7% and 22.6%, respectively, 25 and 30 years after testicular cancer diagnosis. The corresponding population expected risks were 9.3% and 13.1%, respectively. The somewhat higher cumulative risk of second cancer at 25 years for men with seminomas (Fig. 55.7-2) reflects the younger mean age of the patients with nonseminomatous tumors, because the excess cumulative risks were comparable.

Increased risks for cancers of the stomach, bladder and, possibly, pancreas seemed associated with antecedent radiotherapy, whereas leukemia was linked with both prior radiation and chemotherapy. In the past, large doses (mean, 13 to 26 Gy) of radiation could be delivered to the stomach during irradiation of paraaortic lymph nodes for testicular cancer.[85] In prior smaller surveys, a significant eightfold risk of stomach cancer (n = 2) was associated with infra- and supradiaphragmatic irradiation for testicular tumors,[165] and a four- to fivefold risk with was associated with abdominal radiotherapy (n = 10).[166] The study by Travis et al.[85] demonstrated that the increased risks for stomach cancer persisted for at least two decades after diagnosis of testicular cancer. After irradiation for peptic ulcer disease, significant excesses of stomach cancer extend beyond 30 years.[168] A pattern of increasing risk of pancreas cancer with time in the international study,[85] with excesses mainly in testicular cancer patients who received initial radiotherapy, was suggestive of a radiogenic effect, consistent with the location of the pancreas in the radiation field (mean organ dose, 17 to 34 Gy) during therapy for testicular cancer. The pancreas is not considered particularly susceptible to the carcinogenic effects of ionizing radiation,[26] except when very high doses (e.g., on the order of 13 Gy) are given.[168]

Few large, comprehensive studies that quantify the high risk of contralateral testicular cancer (CLTC) have been published,[166,169] which has historically been attributed to common predisposing factors, such as cryptorchism or atrophic testis. Van Leeuwen and colleagues[166] assessed the risk of all second malignancies, including CLTC, in a population-based cohort of 1909 testicular cancer patients for whom complete treatment data and nearly complete follow-up information were available. With a median follow-up of 7.7 years, 20 CLTCs were observed (RR, 35.7; 95% CI, 21.8 to 55.2). Importantly, it appeared that chemotherapy may have reduced the risk of CLTC compared with patients who received radiation or surgery alone.

The increased risk of leukemia after testicular cancer is an order of magnitude lower than that observed in patients with

TABLE 55.7-4. Observed and Expected Numbers of Selected Second Malignant Neoplasms among 1-Year Survivors of Testicular Cancer[a]

	Observed	*Observed to Expected Ratio*	*95% Confidence Interval*
All second cancers[b]	1406	1.4[c]	1.4–1.5
All solid tumors[b]	1251	1.4[c]	1.3–1.4
Esophagus	20	1.3	0.8–2.1
Stomach	93	2.0[c]	1.6–2.4
Small intestine	12	3.2[c]	1.6–5.6
Colon	105	1.3[c]	1.0–1.5
Rectum	77	1.4[c]	1.1–1.8
Liver, gallbladder	26	1.5	1.0–2.1
Pancreas	66	2.2[c]	1.7–2.8
Lung	201	1.0	0.9–1.2
Prostate	164	1.3[c]	1.1–1.5
Kidney	55	1.5[c]	1.1–2.0
Bladder	154	2.0[c]	1.7–2.4
Melanoma	58	1.7[c]	1.3–2.2
Thyroid	19	2.9[c]	1.8–4.6
Bone	6	2.4	0.9–5.3
Connective tissue	22	3.2[c]	2.0–4.8
Non-Hodgkin's lymphoma	68	1.9[c]	1.5–2.4
All leukemia	64	2.1[c]	1.6–2.7
Acute lymphoblastic leukemia	9	5.2[c]	2.4–9.9
Acute nonlymphocytic leukemia	27	3.1[c]	2.0–4.5
Chronic lymphocytic leukemia	7	0.6	0.2–1.2
Chronic granulocytic leukemia	9	0.9	0.4–1.8

[a]Includes 28,843 patients diagnosed with a first primary cancer of the testis who survived 1 or more years.
[b]Numbers exclude contralateral testicular cancers. Category of all solid tumors also excludes lymphohematopoietic disorders.
[c]$P<.05$.
(From ref. 85, with permission.)

Hodgkin's disease. Moderately elevated risks have been observed after chemotherapy,[95,96] but also after irradiation alone.[165,166] Mediastinal nonseminomatous GCTs are known to be associated with an inherent predisposition to develop secondary leukemias,[170] however, such a relationship has not been reported for testicular tumors. In men with mediastinal GCT and leukemia, both cancers contain the cytogenetic abnormality *i(12p)* pathognomonic of GCT,[171] consistent with a common derivation.[170] In contrast, cytogenetic studies of leukemias that follow testicular cancer have displayed alterations characteristic of treatment-related AML.[172–174] Analytic studies that have examined the risk of leukemia after testicular cancer have typically excluded mediastinal GCT.

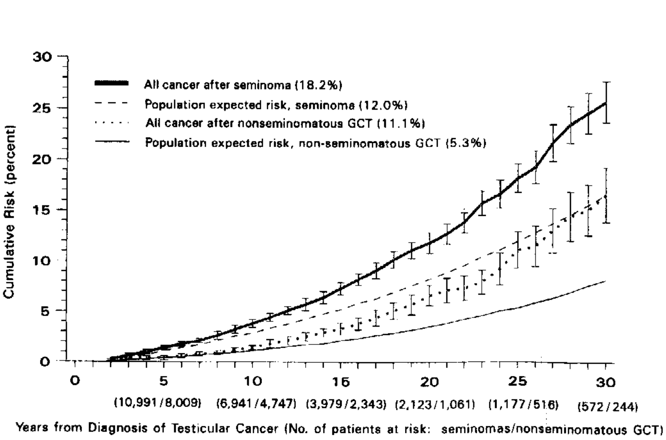

FIGURE 55.7-2. Cumulative risk of second malignant neoplasms among 28,010 1-year survivors of testicular germ cell tumors (GCT). Percentages in parentheses indicate the actuarial risk at 25 years. Within the figure, 95% confidence intervals for point estimates are shown by vertical bars. (From ref. 85, with permission.)

In the early years of platinum-based chemotherapy, the majority of patients received the PVB regimen (cisplatin, vinblastine, bleomycin). The absence of excess leukemia risk after this regimen has been documented in several large studies.[95,166,175–177] In contrast, a number of studies have reported a 20- to 330-fold increased risk of AML after etoposide-containing regimens, which were introduced for the treatment of testicular cancer in the early 1980s.[95,96,172,174] In most of these schedules, etoposide is combined with a platinum compound and other active drugs (bleomycin), but classical alkylating drugs are generally not used. More recently, the IARC concluded that sufficient evidence indicates that etoposide in combination with cisplatin and bleomycin is carcinogenic to humans.[93]

The report by Pedersen-Bjergaard and colleagues[95] was one of the first to note that leukemias induced by epipodophyllotoxins were cytogenetically distinct from classical alkylating agent–related AML. All five cases of AML/MDS were observed in the subgroup of 82 patients who had received cumulative doses of more than 3000 mg/m^2 of etoposide (most patients had three 3-weekly cycles with etoposide, 200 mg/m^2 daily, for 5 days, resulting in a cumulative dose of 3000 mg/m^2). Most etoposide-containing treatment regimens for testicular cancer have used lower cumulative doses of etoposide (up to 2000 mg/m^2) and also a lower dose intensity (100 to 120 mg/m^2). On the basis of the combined data from five studies, Bokemeyer and Schmoll[167] estimated that the relative risk for AML was approximately 20-fold increased in patients treated with conventional etoposide-containing regimens (cumulative dose less than 2000 mg/m^2). Because of the low background incidence of AML in the population, this rather high relative risk translates to a low cumulative risk of 0.6% (95% CI, 0.3 to 0.9%) at 5 years.

In conclusion, patients treated for testicular cancer have less than one-third of the excess risk of second malignancy experienced by patients with Hodgkin's disease. The increased risk of stomach cancer should alert clinicians to the importance of thorough examination of gastrointestinal complaints in patients who received radiotherapy to the paraaortic lymph nodes. Because all reports of increased risks of gastrointestinal cancer have derived from studies in which patients were treated with high doses of radiation, it is important to determine whether smaller risks will follow the lower doses (20 to 25 Gy) that are currently used. Reassuringly, PVB chemotherapy seems to carry a negligible risk of leukemia. Although high-dose etoposide therapy (more than 2000 mg/m^2 in combination regimens) is associated with substantial excess leukemia, cumulative risk after conventional-dose etoposide-containing regimens is low. Radiotherapy regimens for testicular cancer have been modified with the introduction of smaller fields, lower doses, and elimination of prophylactic mediastinal radiation, but the late sequelae of therapy given decades ago continue to emerge. In the future, radiation dose to second cancer sites for which risks are elevated should be estimated in individual patients, along with specific chemotherapeutic agents to further delineate the contribution of treatment factors. Long-term follow-up studies are also needed to evaluate the risk of second solid tumors among testicular cancer patients treated with modern cisplatin-based chemotherapy.[10,81]

OVARIAN CANCER

Because survival for ovarian cancer patients has improved significantly within the last two decades,[148] the study of second primary cancers has assumed increasing clinical importance.[178] The site-specific risk of solid tumors after ovarian cancer has been quantified in a large population-based study of more than 32,000 women with ovarian cancer, including 4402 10-year survivors.[178] Almost 1300 second cancers (n = 1296) were reported, representing a significantly increased risk (O/E = 1.3; 95% CI, 1.2 to 1.4). Significant excesses were observed for cancers of colon (O/E = 1.3), rectum (O/E = 1.4), breast (O/E = 1.2), and bladder (O/E = 2.1), as well as leukemia (O/E = 4.2). Ocular melanoma (O/E = 4.5) was also significantly increased. Secondary leukemia appeared to be linked with antecedent chemotherapy, whereas radiotherapy was associated with cancers of connective tissue, bladder and, possibly, pancreas. The risk of solid tumors was elevated during all follow-up intervals, including 10 to 14 years (O/E = 1.3) and 15 years or more (O/E = 1.3) after ovarian cancer. Fifteen-year survivors experienced significant excesses of cancers of pancreas, bladder, and connective tissue. The cumulative risk of second cancers at 20 years was 18.2% compared with a population-expected risk of 11.5% (Fig. 55.7-3).

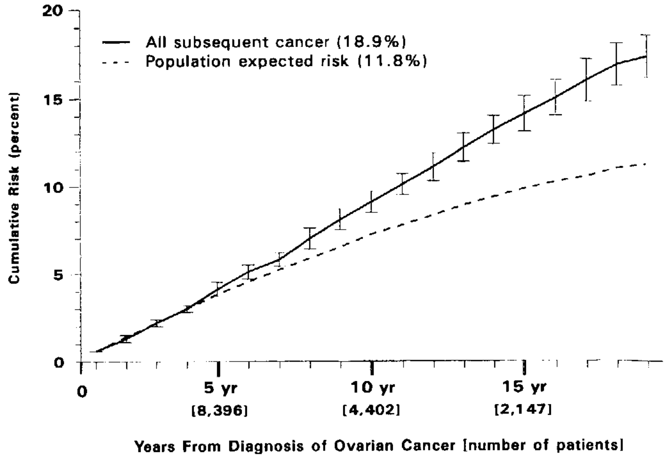

FIGURE 55.7-3. Cumulative risk of second malignant neoplasms among 32,251 2-month survivors of ovarian cancer. Percentages in parentheses are actuarial risk at 20 years. Within the figure, 95% confidence intervals for point estimates are shown by vertical bars. (From Travis LB, Curtis RE, Boice JD Jr, et al. Second malignant neoplasms among long-term survivors of ovarian cancer. *Cancer Res* 1996;56:1564, with permission.)

In an analytic study of bladder cancer after ovarian cancer, Kaldor et al.[119] found increased risks after radiotherapy only (RR, 1.9; 95% CI, 0.8 to 4.9) compared with patients treated with surgery alone. Cyclophosphamide-based chemotherapy, with or without radiotherapy, was associated with a fourfold risk.

Large risks of AML and preleukemia have been documented after ovarian cancer, and they have been linked to therapy with melphalan,[17,92] cyclophosphamide,[17,80,92] and chlorambucil.[17,179] In one large population-based study of more than 28,000 ovarian cancer patients in whom 96 leukemias were diagnosed, platinum-based combination chemotherapy was associated with a significantly increased fourfold risk compared with women who received neither alkylating drugs nor radiotherapy.[81] Excesses of leukemia increased with increasing cumulative platinum dose (P trend for dose <.001) (Table 55.7-5).

Although the platinating agents were frequently given in combination with cyclophosphamide, doxorubicin, or both, a multivariate model that took into account the cumulative amount of these drugs did not provide an improved fit to the data (P >.5) compared with a model that took into account only dose categories of platinum. Although the risk of leukemia after platinum-based chemotherapy tended to be somewhat higher among younger patients, differences in relative risk according to age were not significant (P for heterogeneity = .48). Radiotherapy without chemotherapy (mean bone marrow dose, 13.4 Gy) did not increase the risk of leukemia,[81] but few women received radiation alone. Patients given radiotherapy and platinum-based chemotherapy, however, had a significantly (P = .006) higher risk of leukemia than those who received platinum-based chemotherapy alone in a multivariate model adjusted for cumulative amount of the drug. A dose response was observed for platinum among women treated and not treated with radiotherapy, with risks higher within the radi-

TABLE 55.7-5. Risk of Leukemia According to the Cumulative Dose of Platinum, Duration of Therapy, and Specific Drug[a]

Dose and Duration	*Number of Patients with Leukemia*	*Number of Matched Control Patients*	*Median Value in Controls*[b]	*Relative Risk (95% Confidence Interval)*[c]
All platinum drugs				
Dose[d]				
<500 mg	4	30	418 mg	1.9 (0.5–7.9)
500–749 mg	5	28	600 mg	2.1 (0.6–8.0)
750–999 mg	7	25	896 mg	4.1 (1.1–14.8)
>1000 mg	11	20	1230 mg	7.6 (2.3–25.3)[e]
Duration				
<6 mo	3	36	5.4 mo	1.2 (0.3–5.5)
6–12 mo	16	49	8.5 mo	4.3 (1.4–12.9)
>12 mo	8	18	14.2 mo	7.0 (1.8–26.6)[f]
Specific drug				
Cisplatin	19	85	600 mg	3.3 (1.1–9.4)
Carboplatin	3	9	3300 mg	6.5 (1.2–36.6)
Both	5	9		9.0 (2.2–37.6)
Cisplatin			720 mg	
Carboplatin			2200 mg	

[a]The data are limited to 27 patients with leukemia and 103 controls who receive platinum-based chemotherapy without melphalan.
[b]The values shown are median cumulative doses of platinum and the median duration of therapy among controls.
[c]The reference group consisted of six patients with leukemia and 94 controls who were not exposed to platinum derivatives of other alkylating drugs.
[d]Cumulative amounts of carboplatin were divided by 4 to convert them to cisplatin-equivalent doses.
[e]P for trend <.001.
[f]P for trend = .001.
(From ref. 81, with permission.)

ation group; in all of the latter patients, radiotherapy had been given as part of initial treatment. It is unlikely that women newly diagnosed with ovarian cancer would receive both platinum and radiotherapy in view of modern treatment recommendations.[180] However, the possibility that the risk of leukemia after treatment with platinum might be increased by radiotherapy should be investigated among patients with other cancers, especially cancers of bladder and head and neck, given therapeutic strategies to increase dose intensities of both modalities in the treatment of these tumors.[181]

The risk of leukemia associated with the cumulative dose of melphalan[17,92] and, importantly, route of administration[81] also has been evaluated among women with ovarian cancer. In the largest study to date,[81] significant excesses of leukemia followed intravenous (RR, 22.9) and oral (RR, 9.0) melphalan, and risks increased with increasing cumulative dose and duration of therapy. Intravenous melphalan was six times more leukemogenic than platinum.

In conclusion, survivors of ovarian cancer experience significantly increased risks of secondary leukemias and solid tumors. Despite the elevated relative risk of leukemia after modern platinum-based chemotherapy for ovarian cancer, the absolute risk is small.[81] Of 10,000 ovarian cancer patients treated for 6 months with cumulative doses of cisplatin between 500 and 1000 mg or 1000 mg or more and followed for one decade, an excess of 21 and 71 leukemias, respectively, was predicted based on observed risks.[81] Thus, Travis and colleagues[81] concluded that the significant improvement in clinical response provided by platinum-based treatment for advanced ovarian cancer, with 5-year survival rates of up to 20% to 30%,[180,182] far exceeded the relatively small excesses of leukemia. Further interdisciplinary investigations are needed to elucidate the carcinogenic risks associated with modern therapies for ovarian cancer and with shared susceptibility mechanisms, including genetic and reproductive factors. Meanwhile, in proposing recommendations for the follow-up and management of women with ovarian cancer,[180] it is important to recognize their long-term predisposition to an array of second cancers.

BREAST CANCER

Numerous studies have demonstrated that women with breast cancer are at a three- to fourfold increased risk of developing a new primary cancer in the contralateral breast.[183,184] Significant excesses relative to the general population also have been observed for cancers of the ovary,[183,185] uterus,[183,186,187] lung,[58,183,185,188,189] esophagus,[190] colon-rectum,[183,185,187] connective tissue,[183,189,191–193] and thyroid,[183,185] as well as melanoma[183,189] and leukemia.[101,185,189,194] For some of these cancers, such as those of the contralateral breast, ovary, and uterus, and possibly melanoma, the excesses may be fully or partly explained by a common etiology (e.g., genetic predisposition or hormonal risk factors). Other excess risks may be treatment-related or reflect the interaction of several factors. Adjuvant chemotherapy, hormonal treatment, and radiotherapy, and combinations of these modalities, are being administered to a growing proportion of breast cancer patients. In view of the proven therapeutic benefit of these treatments[195,196] and the prolonged life expectancy of those treated, it has become exceedingly important to evaluate the carcinogenic potential of adjuvant treatment.

Contralateral breast cancer accounts for 40% to 50% of all second tumors in women with breast cancer,[183] and the 15-year cumulative risk of developing contralateral disease amounts to 10% to 13%.[197,198] With this high risk, even small effects of treatment may have a large impact in terms of absolute numbers of contralateral breast cancers. The effect of radiation treatment for the initial breast cancer was evaluated in two large case-control studies in Connecticut and Denmark that involved 655 and 529 women with contralateral breast cancer, respectively. The mean radiation doses to the contralateral breast were estimated at 2.8 and 2.5 Gy, respectively.[22,199] Both studies found that radiotherapy did not contribute to the high risk of contralateral disease among women treated after the age of 45. In the Connecticut study, however, significantly elevated risks were observed for women who underwent irradiation before the age of 45, with a radiation-associated relative risk of 1.9 among those who survived for at least 10 years.[22] Significant excess risk in women irradiated at a young age was not found in the Danish study, possibly because it included fewer women younger than 45 years of age.[199] Based on the Connecticut study, Boice and associates[22] estimated that approximately 11% of all second breast cancers in women irradiated before age 45 could be attributed to radiotherapy.

Several large studies have shown that hormonal treatment with tamoxifen reduces the risk of contralateral breast cancer by approximately 40%.[186,187,195,200,201] Data collected by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), based on 37,000 women from 55 trials, demonstrated that longer durations of tamoxifen use were associated with greater reductions in risk, such that 1 year, 2 years, and 5 years of treatment produced risk reductions of 13%, 26%, and 47%, respectively.[195] It is not yet known whether the protective effect of tamoxifen against contralateral disease persists over prolonged follow-up periods (more than 10 years). Some studies have provided evidence that adjuvant chemotherapy may also reduce the risk of contralateral breast cancer, a phenomenon that is likely to be mediated through drug-induced premature ovarian failure.[153,196,202]

Several studies have assessed the risk of leukemia after adjuvant chemotherapy and radiotherapy for breast cancer. The relationship between AML risk and drug dose was examined in detail in the large case-control study by Curtis and associates.[20] These investigators identified 90 cases of leukemia or MDS among 82,700 women diagnosed with breast cancer between 1973 and 1985 in five areas of the United States. Compared with patients treated without alkylating agents and irradiation, the risk of AML was significantly elevated after locoregional radiotherapy alone (RR, 2.4), after treatment with alkylating agents alone (RR, 10.0) and after treatment with alkylating agents in combination with radiotherapy (RR, 17.4). The risk of AML associated with combined modality treatment was significantly greater than that for alkylating agents alone ($P = .02$). The study included large numbers of women who had been treated with only one alkylating agent, including cyclophosphamide. Cumulative cyclophosphamide doses of less than 20 g were associated with an approximately twofold, nonsignificant increase in risk (compared with women not exposed to alkylating agents), whereas women treated with 20 g or more had a 5.7-fold risk of AML (95% CI, 1.6 to 20.6). Women who received melphalan experienced tenfold risks of AML compared with women treated with cyclophosphamide ($P < .001$). After adjustment for the effects of chemotherapy, the risk of AML increased significantly with higher doses of radiation to the active bone marrow, with a sevenfold risk increase for patients who received 9 Gy or more (compared to patients not treated with radiotherapy).

Present-day adjuvant treatment of early breast cancer is in several ways different from the treatments evaluated in this large study by Curtis et al.[20] In the 1980s, the cumulative doses of cyclophosphamide were reduced [approximately 12 to 15 g with six standard cycles of CMF (cyclophosphamide, methotrexate, and fluorouracil) or FAC (fluorouracil, doxorubicin, and cyclophosphamide)]. Regional radiotherapy is less frequently used. On the basis of their data, Curtis and associates[20] estimated that, among 10,000 patients with breast cancer treated for 6 months with a cyclophosphamide-based regimen and followed for 10 years, an excess of only five cases of treatment-related AML would be expected to develop.

The low risk of AML after CMF-based chemotherapy was confirmed by the Milan Cancer Institute[203] and the Eastern Cooperative Oncology Group,[204] with cumulative risks of AML of 0.23% at 15 years and 0.18% at 7 years, respectively. Thirty-nine percent of women treated with CMF-based chemotherapy in the Milan series[203] also received doxorubicin, and no clear evidence indicated a synergistic effect of cyclophosphamide and doxorubicin on leukemia risk. Radiation therapy (applied only after breast-conserving surgery) did not add to the risk of AML. The University of Texas M. D. Anderson Cancer Center has reported a higher risk of leukemia after standard dose–intensity FAC treatment. Fourteen cases of leukemia were observed among 1474 patients, for an estimated cumulative risk of 1.5% (95% CI, 0.7 to 2.9) at 10 years. The risk of AML was significantly higher when chemotherapy was given in combination with radiotherapy (2.5% vs. 0.5%).[103]

There has been an increasing trend toward the use of dose intensification strategies in chemotherapy protocols for breast cancer. Typically, these regimens contain high-dose cyclophosphamide in combination with one of the anthracyclines (doxorubicin or 4-epidoxorubicin) and other active drugs. The risk of AML associated with such dose-intensive chemotherapy has not yet been quantified, but evidence suggests that the combination of anthracyclines and alkylating agents (including cisplatin) may be leukemogenic.[101] With the increasing tendency to administer high doses of cytotoxic drugs accompanied by bone marrow support, there is certainly a strong need to closely monitor the subsequent risk of AML.

Patients treated with CMF-based chemotherapy have not been reported to be at increased risk of solid tumors.[203,205] More prolonged follow-up, however, is needed to evaluate possible carcinogenic effects 15 years or more after treatment.

Conclusive evidence has emerged that tamoxifen is associated with a moderately increased risk of endometrial cancer.[186,187,195,200,206–210] The consistent results across studies with different designs, the duration-response relationship observed in several investigations,[206,207,209,211,212] and the established estrogen-agonist effects of tamoxifen on the endometrium[213–215] strongly support a causal relationship.[208] The individual studies, which are summarized in Table 55.7-6, show that the use of tamoxifen for 2 years is associated with an approximately twofold increased risk of endometrial cancer, whereas use for 5 or more years produces four- to eightfold excess risks. Although the risk estimates in some studies may be affected by a certain degree of detection bias as a result of gynecologic examinations in women with side effects from tamoxifen, the magnitude of the observed risk is unlikely to be explained by such bias.[208] Furthermore, the analysis of the EBCTCG not only shows increased incidence of endometrial cancer in women randomized to tamoxifen treatment (as compared to women not randomized to tamoxifen) but also significantly increased

TABLE 55.7-6. Risk of Endometrial Cancer after Tamoxifen Therapy in Women with Breast Cancer

Author[a]; Design	*Number of Breast Cancers*	*Number of Endometrial Cancers (Number in Tamoxifen Users)*	*Dosage Evaluated*	*Duration of Tamoxifen Use*	*Relative Risk (95% Confidence Interval)*
Fisher et al. 1994[186]; clinical trial	4063	24 (23)	20 mg	Planned: ≥5 y	Tamoxifen vs. control: 7.5 (1.7–32.7) Tamoxifen vs. general population: 2.2[b] Tamoxifen vs. control other trial: 2.3[b]
Rutqvist et al. 1995[187]; clinical trial	4914	42 (34)	30–40 mg	48 wk–5 y	Any: 4.1 (1.9–8.9)
EBCTCG 1998[195]; clinical trials	36,689	124 (92)	Mostly 20 mg	1, 2, or 5 y	Ever use: 2.6 (2.2–2.9) 5 y: 4.2 (P<.001)
Fisher et al. 1998[210]; prevention trial	13,388	51 (36)	20 mg	1–5 y	Any: 2.5 (1.4–5.0)
Curtis et al. 1996[200]; cohort (SEER-based)	87,323	457 (73)	Unknown	Unknown	Any tamoxifen vs. general population: 2.0 (1.6–2.6) No tamoxifen vs. general population: 1.2 (1.1–1.4)
Sasco et al. 1996[207]; case-control	NA	43 (29)	Mostly 20 mg	Varied	Any: 1.4 (0.6–3.5) ≥5 y: 3.5 (0.9–12.7) Trend with duration: P = .0001
Mignotte et al. 1998[212]; case-control	NA	135 (91)	20–40 mg	Varied	Ever use: 3.1 (1.1–8.7) ≥5 y: 10.7 (3.4–34) Trend with duration: P = .0001
Bernstein et al. 1999[209]; case-control	NA	324 (146)	Mostly 20 mg	Varied	Ever use: 1.5 (1.1–2.2) ≥5 y: 4.1 (1.7–9.5) Trend with duration: P = .0002
Bergman et al. 1998[211]; case-control	NA	299 (108)	20–40 mg	Varied	Ever use: 1.5 (1.1–2.0) ≥5 y: 6.6 (2.2–19.7) Trend with duration: P<.001

EBCTCG, Early Breast Cancer Trialists' Collaborative Group; NA, not available; SEER, Surveillance, Epidemiology and End Results.
[a]Several early reports are not presented because the data are included in larger or updated studies presented here.[187,209,211]
[b]Because the incidence of endometrial cancer appeared to be unexpectedly low among placebo-treated women, the investigators reestimated the risk associated with tamoxifen, using population-based rates and information from another trial. However, the resulting risk estimates of 2.2 and 2.3, respectively, are less valid than the estimate based on the endometrial cancer rate in placebo-allocated controls (relative risk, 7.5) because (a) regardless of treatment, a population of breast cancer patients entered into a clinical trial may have different endometrial cancer rates than the general population; and (b) the rates used were from a different geographic area, a different period, or both.[208]

mortality due to endometrial cancer.[195] From Table 55.7-6, it is clear that elevated risks of endometrial cancer have been observed after daily tamoxifen dosages of 20 mg, 30 mg, or 40 mg. In the Netherlands case-control study, which included different dose intensities, daily dosage did not affect endometrial cancer risk in a model accounting for duration of use, and the duration-response trends were similar, with daily doses of 40 mg, or 30 mg or less.[211] Very few studies have addressed the risk for ex-users. In three investigations,[209,211,212] recent and former users of tamoxifen were found to experience very similar increases in risk; however, only a few patients had discontinued tamoxifen more than 2 years before the diagnosis of endometrial cancer.

Only two studies have addressed the combined effects of tamoxifen and other risk factors for endometrial cancer.[209,211] In the largest study conducted to date, Bernstein and colleagues[209] reported that women who previously used estrogen replacement therapy experienced greater increases in endometrial cancer risk associated with tamoxifen use than women not exposed to estrogen replacement therapy. Furthermore, the effects of tamoxifen on endometrial cancer risk were stronger among heavy women than among thin women. In the Dutch study, however, body weight did not modify the increased risk associated with tamoxifen use.[211]

An important question is whether the clinicopathologic characteristics and ultimate prognosis of endometrial cancers after tamoxifen treatment are different from those in patients not treated with tamoxifen. In four small studies, the stage distribution and histologic features of endometrial cancers in tamoxifen-treated women were not remarkably different from those diagnosed in nontreated women.[186,200,206,216] Magriples and colleagues,[217] however, reported a higher frequency of poorly differentiated and high-grade tumors with a poor prognosis in tamoxifen-treated patients. In the Dutch study, which included 309 patients with endometrial cancer after breast cancer, endometrial tumors of FIGO stage III and IV occurred

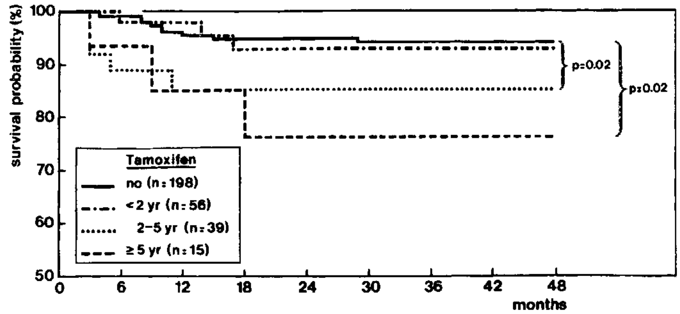

FIGURE 55.7-4. Actuarial endometrial cancer–specific survival according to duration of tamoxifen use. (From ref. 211, with permission.)

more frequently among long-term tamoxifen users (2 or more years) than in nonusers (17% vs. 5%, $P = .006$). Based on a centralized review of diagnostic pathology slides, long-term tamoxifen users more often developed malignant mixed mesodermal tumors or sarcomas of the endometrium than did nonusers (15% vs. 3%, $P = .02$). Furthermore, the tumors diagnosed among long-term tamoxifen users were more often p53-positive and estrogen receptor–negative. Figure 55.7-4 shows that the 3-year actuarial endometrial cancer–specific survival in this study was significantly worse for long-term tamoxifen users than for nonusers, largely due to the less favorable tumor characteristics associated with tamoxifen use.[211] The association between tamoxifen use and specific clinicopathologic and molecular characteristics of subsequent endometrial cancer deserves further investigation in large studies.

Animal experiments have shown that tamoxifen can act as a hepatic carcinogen in rats.[218,219] However, no increased risk of hepatocellular cancer in tamoxifen-treated patents has been observed to date.[186,187,195,200] In the large metaanalysis of the EBCTCG, women randomized to tamoxifen had a slightly lower mortality from primary liver cancer than the control group.[195] The joint analysis of Scandinavian tamoxifen trials showed an elevated risk of gastrointestinal cancer after tamoxifen use (RR, 1.9; 95% CI, 1.2 to 2.9)[187]; however, the excess risk was due to colorectal and stomach cancer, not liver cancer. Furthermore, a study from the SEER program found that tamoxifen was associated with a 50% increased risk of colorectal cancer in the period 5 or more years after diagnosis.[220] No such risk increase was observed in the EBCTCG data.[195]

Increased risks of lung cancer after breast cancer have been largely attributed to radiotherapy.[58,188,221] No appreciable risk increase has been observed within 10 years of treatment, but two- to threefold elevated risks have been reported in 10-year survivors.[58,188,189] The association between breast radiotherapy and subsequent lung cancer risk was found to be stronger for the ipsilateral lung, which supports a radiogenic effect.[188,221] Using individual patient dosimetry, Inskip and associates[58] assessed the effect of radiation dose to the lung in a case-control study of lung cancer after breast cancer. Sixty-one lung cancers were identified among 8976 10-year survivors of breast cancer treated in Connecticut between 1935 and 1971. Mean radiation dose was 15 Gy to the ipsilateral lung and 4.6 Gy to the contralateral lung. A nonsignificant increase in lung cancer risk was noted with increasing radiation dose to the affected lung, with an approximate threefold excess risk for patients who received 5 to 10 Gy. Risk seemed to level off at doses higher than 10 Gy, as has been observed in a similar study of lung cancer after Hodgkin's disease.[38] The results were used to predict that, among 10,000 10-year survivors of breast cancer who received an average lung dose of 10 Gy, approximately nine radiogenic lung cancers would be expected to develop per year. Current radiotherapy practices for breast cancer involve high-energy megavoltage treatment to localized radiation fields, which results in considerably lower lung doses than the orthovoltage and cobalt-60 radiation treatments used in the studies described above. The risk of radiogenic lung cancer should be correspondingly lower (i.e., approximately one excess lung cancer per 10,000 women-years per Gy) beginning 10 years after radiotherapy.[58] In one study, smokers were found to be at greater risk of radiation-associated lung cancer than nonsmokers.[221,222]

Heightened concern with regard to the subsequently increased risk of angiosarcomas in the irradiated conserved breast has been expressed.[192,193] In a nationwide study, 21 Dutch patients with angiosarcoma of the breast after breast-conserving treatment and localized radiation were reported, with a median latency of 6 years.[193] The incidence of angiosarcoma in the breast was estimated at 1.6 per 1000 patients treated with breast conservation per year. Although the absolute excess risk is small, the relative risk is more than 1000-fold increased in comparison with the incidence of this very rare disease in the general population. In a nationwide case-control study in Sweden[191] of 116 women with soft tissue sarcoma after a diagnosis of breast cancer between 1958 and 1992, it was found that the risk of sarcomas other than angiosarcoma increased with the amount of radiation, but stabilized at high doses. The study included 40 angiosarcomas (located mostly in the ipsilateral arm, with only two cases in conserved breasts). The risk of angiosarcoma was 9.5-fold increased in women with lymphoedema of the arm, but radiotherapy was not a risk factor.

In conclusion, only part of the elevated risk of second malignancies after breast cancer is due to treatment. The intrinsically increased risk of developing a contralateral tumor is unlikely to be meaningfully affected by current radiotherapy for the initial breast cancer, whereas tamoxifen reduces the risk of contralateral disease. Standard dose–intensity CMF treatment is associated with a low excess risk of leukemia, whereas conventional FAC treatment may be associated with a somewhat higher risk. Whether the risk of leukemia will increase further with the introduction of dose-intensification strategies should be explored. Although tamoxifen causes a moderate increase in endometrial cancer risk, the proven clinical benefit of this drug in controlling breast cancer[195] far outweighs the excess morbidity and mortality due to endometrial cancer. Clinicians should be alert to signs and symptoms in women taking tamoxifen, and long-term users should be advised to seek prompt gynecologic evaluation on the development of symptoms. The effectiveness of screening for endometrial cancer has not been demonstrated. Consequently, outside of research settings, there is no basis for regular gynecologic examinations in asymptomatic patients taking tamoxifen. The absolute excess risk of lung cancer is likely to be small with current radiotherapy techniques for breast cancer. Nevertheless, there is ample reason to advise breast cancer patients to stop smoking when they receive radiation treatment.

PEDIATRIC MALIGNANCIES

Survival rates for children with cancer have improved substantially since the late 1970s. Consequently, a rapidly growing young population is subject to the late effects of cancer treatment for life. The overall pattern of second cancer risk in the population of childhood cancer survivors has been described in several large studies.[51,62,223–225] Most recently, de Vathaire and colleagues[51] reported on the long-term risk of second cancer in a cohort of 4400 3-year survivors of childhood cancer (excluding patients with leukemia) treated in eight centers in France and the United Kingdom. The risk of second solid malignancies was increased 9.2-fold compared to the general population (95% CI, 7.6 to 11.0), and the absolute excess risk was 188 cases per 10,000 patients per year. The 30-year cumulative risk was 7.7% (95% CI, 5.0 to 8.2%). Olsen and collaborators[223] observed a 3.6-fold increased risk of second malignancy (95% CI, 3.1 to 4.1) in 30,880 children diagnosed with cancer and reported to the population-based cancer registries of five Nordic countries between 1943 and 1987. The cumulative risks of developing a second tumor within 25 years were 3.7% and 3.5%, respectively. Among 9170 2-year survivors of childhood cancer who were treated by members of the U.S. Late Effects Study Group (LESG), the risk of developing a second malignancy was increased 15-fold compared to the general population (95% CI, 13 to 17), with a cumulative incidence of 12.1% at 25 years.[62] The lower risks in the European studies may be related to their population-based nature (less selection),[223,224] to treatment differences between Europe and the United States, and to differences between the study populations with respect to calendar years of diagnosis and length of follow-up. In all studies, the largest relative risks were found for second primary bone tumors (133-fold and 43-fold increased risks in the LESG[225] and British cohort,[224] respectively) and second soft tissue sarcoma. Large risks were also observed for second thyroid cancer, gastrointestinal cancers, brain tumors, and leukemia. Retinoblastoma is the initial malignancy that has been consistently associated with the highest risk of subsequent tumors.[51,62,223,224]

Only a portion of the excess second cancer risk in survivors of childhood cancer is related to treatment. Retinoblastoma is the prototype of an initial malignancy in which genetic factors are responsible for a large part of subsequent cancers. Familial retinoblastoma is caused by inherited mutations of the RB1 tumor suppressor gene, which has been localized to the long arm of chromosome 13q14.[226,227] Approximately 80% of hereditary retinoblastoma patients have bilateral disease. In a long-term follow-up study of 1604 1-year survivors of retinoblastoma diagnosed between 1914 and 1984 (median follow-up, 20 years), the incidence of second cancers as well as risk factors for second malignancy were evaluated.[69] Overall, the risk of second malignancy was increased 17-fold compared to the general population expectation. The excess risk was restricted to the 961 patients with hereditary retinoblastoma (RR, 30; 95% CI, 26 to 47), with strongly increased relative risks for cancers of the bone, soft tissues, nasal cavities, and brain, and for melanoma (relative risks of 446, 103, more than 100, 14, and 51, respectively). No significantly increased risk of second malignancy was observed among 643 nonhereditary retinoblastoma patients (RR, 1.6; 95% CI, 0.7 to 3.1). Fifty years after retinoblastoma diagnosis, the cumulative risk of second primary cancer was 51.0% (± 6.2%) in hereditary cases, and only 5.0% (± 3.0%) in nonhereditary cases. As shown in Figure 55.7-5, radiotherapy significantly increased the risk of second cancers in patients with hereditary retinoblastoma (50-year cumulative risk of 58% vs. 27% in nonirradiated hereditary patients). Radiotherapy did not significantly affect risk in nonhereditary retinoblastoma patients.[69] In a case-control investigation that included 52 patients with bone sarcoma, 31 with soft tissue sarcoma, and 89 controls without sarcoma, Wong and associates[69] also collected individual radiation dosimetry data. For all sarcomas combined, risk was significantly elevated at all dose levels, even at 5.0 to 9.9 Gy, and a significant increase in risk was observed with increasing radiation dose to the site of tumor (relative risk of 11 for doses of 60 Gy or more as compared with doses of 0 to 4.9 Gy) For the first time in humans, a radiation dose-response relationship was also demonstrated for soft tissue sarcoma, with a 12-fold risk increase at doses of 60 Gy or greater. Osteosarcomas and soft tissue sarcomas developing after hereditary retinoblastoma harbor similar RB1 mutations as those found in retinoblastoma.[228,229] Radiation is thus likely to cause somatic mutations needed to produce sarcomas in carriers of germline RB1 mutations.

Wilms' tumor is another example of an initial malignancy in which genetic predisposition contributes to the excess risk of second cancers.[225] The National Wilms' Tumor Study Group reported on the second malignancy experience of 5278 patients followed for an average of 7.5 years.[104] Forty-three second malignancies were observed, with an overall relative risk of 8.4 (95% CI, 6.1 to 11.4). The 15- and 20-year cumulative risks of developing a second tumor were 1.6% and 3.8%, respectively. Significant excesses were seen for leukemia (RR, 7.0), lymphoma (RR, 9.0), osteosarcoma (RR, 19), soft tissue sarcoma (RR, 22), and hepatocellular carcinoma (RR, 56)[104] (N. E. Breslow, written communication, April 1996). Among patients not treated with radiation or doxorubicin, risk of second malignancy was increased threefold, reflecting genetic predisposition.[104] Each 10 Gy of abdominal irradiation was found to increase second malignancy risk by 43% in the absence of doxorubicin and by 78% in its presence. Treatment with both doxorubicin and more than 35 Gy of abdominal irradiation was associated with a relative risk of 36 (95% CI, 16 to 72).[104] Because the small numbers of individual second malignancies precluded an analysis by site, it is unclear whether these results apply equally for leukemia, sarcoma, and other tumors.

ALL, the most common malignancy in childhood, is also associated with an increased risk of subsequent cancer. In a series of 9720 childhood ALL patients treated in trials of the Children's Cancer Study Group between 1972 and 1988, the risk of developing a second malignancy was increased 6.9-fold as compared with the general population.[230] The associated 10- and 15-year cumulative risks were 1.5% and 2.5%, respectively. In a multicenter Italian study including 1664 ALL patients, the relative risk of all second cancers was 13.6, with cumulative risks of 2.6% and 4.5%, respectively, at 10 and 15 years since the completion of initial treatment.[231] In both studies, the largest excess was observed for central nervous system tumors, with

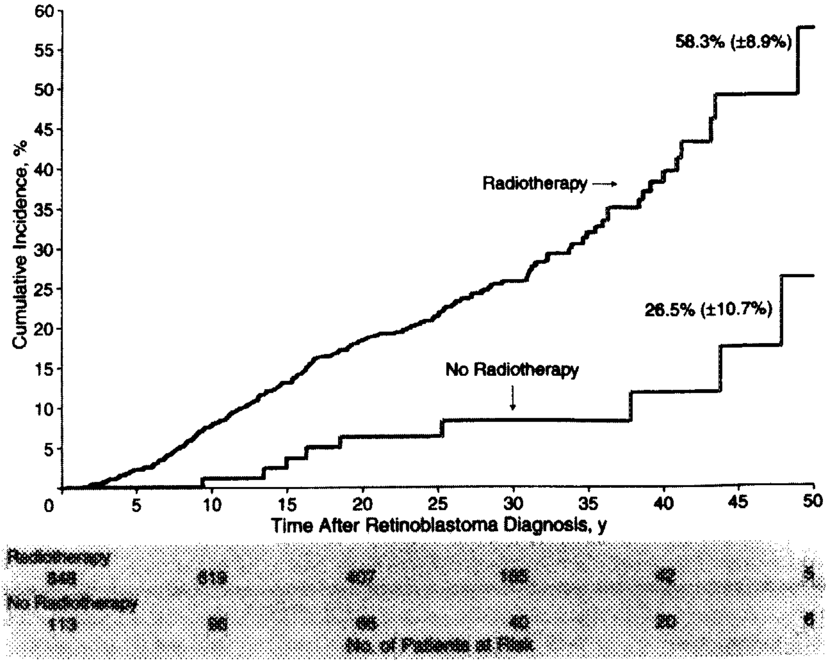

FIGURE 55.7-5. Cumulative incidence (± s.e.) of second cancers after diagnosis of retinoblastoma in 961 patients with hereditary disease, by radiation treatment. (From ref. 69, with permission.)

relative risks of 22[230] and 52.[231] Most brain tumors were high-grade astrocytomas or glioblastomas, and all occurred in children who had previously received radiotherapy, mostly cranial irradiation with doses ranging from 18 to 24 Gy. A study of 1612 patients with ALL from St. Jude Children's Research Hospital, with long-term follow-up data (median follow-up, 16 years), demonstrated an excess of high-grade gliomas during early follow-up (up to 10 years after diagnosis), whereas an increased risk of low-grade brain tumors was observed at later follow-up intervals.[232] The risk of developing a brain tumor was significantly increased with increasing cranial radiation dose, with 20-year cumulative risks of 1.0%, 1.7%, and 3.2% for patients who received radiation doses of 10 to 21 Gy, 21 to 30 Gy, and 30 Gy or more, respectively.

During the 1990s, prophylactic cranial radiotherapy has been largely replaced by intrathecal methotrexate. The number of intrathecal methotrexate administrations was not related to the risk of brain tumors,[232] but few children treated without cranial radiation were followed for more than 15 years. In two studies,[230,232] risk of central nervous system tumors was significantly higher in children 5 years of age or younger at first treatment.

Several very large studies of ALL survivors have reported negligible risks of AML after chemotherapy regimens that contain cyclophosphamide, anthracyclines, or both.[230,231,233] In contrast, very high risks of AML have been reported for children treated with epipodophyllotoxin-containing regimens. Pui and associates[97] were the first to report on the risk of AML in 734 children with ALL who received maintenance treatment according to different schedules of epipodophyllotoxin administration at St. Jude Children's Research Hospital. AML developed in 21 children, with an overall cumulative risk of 3.8% at 6 years follow-up. The schedule of epipodophyllotoxin treatment appeared to be a crucial factor in determining AML risk. Patients who received weekly or twice-weekly doses of teniposide (with or without etoposide), were at an approximately 12 times greater risk of AML than patients treated only during remission induction, or every 2 weeks during maintenance treatment. Several subgroups of patients in this study were exposed to other potentially leukemogenic factors, such as cyclophosphamide and cranial irradiation. The strongest evidence that the excess risk of AML was due to epipodophyllotoxin treatment came from comparing two subgroups that differed only in schedule of epipodophyllotoxin administration. Among 84 patients who received epipodophyllotoxins weekly, the risk of AML was clearly and significantly increased (12.4% at 6 years; 95% CI, 6.1% to 24.4%) compared with 148 patients who received the agents every other week (1.6% at 6 years; 95% CI, 0.4% to 6.1%; $P = .01$). Cumulative dose did not show enough variation within the study groups to reliably assess its effect. Compelling evidence for a causal link between epipodophyllotoxin therapy for ALL and the development of AML was also provided by Winick and associates.[234]

Elevated risk of AML also has been reported after a number of other childhood malignancies, especially lymphomas.[57,62,105,223,235,236] Two case-control studies addressed the effects of radiation dose and amount of chemotherapy on the risk of AML in children treated for various malignancies.[18,105] A significant dose-response relationship between total dose of alkylating agents and AML risk was observed in both studies. The Late Effects Study Group[18] found no association between leukemia risk and radiation dose to active bone marrow. In contrast, using similar methods of estimating bone marrow dose, Hawkins and colleagues[105] observed a highly significant trend, with an approximately 20-fold increased risk for patients receiving 15 Gy or more (compared to patients not treated with radiotherapy). These discrepant results may be explained by differences between the studies in the pattern of first cancers and in therapeutic practices. It is possible that the patients in the British study received lower radiation doses to larger vol-

TABLE 55.7-7. A Case-Control Study of Second Primary Bone Cancer in Relation to Radiation Dose and Cumulative Exposure to Alkylating Agents

Radiation Dose, cGy	*Number of Patients* Cases (n = 59)	Controls (n = 220)	*Relative Risk (95% CI) Adjusted for Alkylating Agent Exposure*	*P Value*
0	10	61	1.0	—
1–999	13	79	0.7 (0.2–2.2)	$P = .537$
1000–2999	7	15	12.4 (0.9–163.3)	$P = .055$
3000–4999	15	7	93.4 (6.8–1285.4)	$P < .001$
≥5000	5	6	64.7 (3.8–1103.4)	$P = .004$
Incomplete information	9	52	—	—
Test for linear trend	—	—	—	$P < .001$
Total Cumulative Exposure to Alkylating Agents, mg/m²	*Number of Patients* Cases (n = 59)	Controls (n = 220)	*Relative Risk (95% CI) Adjusted for Radiation Exposure*	*P Value*
0	37	164	1.0	—
1–9999	6	21	1.3 (0.3–6.0)	$P = .698$
10,000–19,999	7	20	3.0 (0.4–21.7)	$P = .278$
≥20,000	7	8	3.3 (0.8–13.8)	$P = .107$
Incomplete information	2	7	—	—
Test for linear trend	—	—	—	$P = .080$

CI, confidence interval.
(Adapted from ref. 61, with permission.)

umes of bone marrow, which, for a specified dose, might result in less cell kill and a greater susceptibility to leukemogenic transformation.[105] The case-control study in the United Kingdom[105] included ten cases of secondary AML after epipodophyllotoxin treatment, mostly for pediatric NHL. It is of interest that, at much lower cumulative doses than used in the St. Jude Children's Research Hospital study,[97] a steep increase in AML risk was noted with increasing dose of epipodophyllotoxins. Another striking difference between the two studies was that the strong dose-response relationship in the British study was observed for regimens in which the epipodophyllotoxins were given less frequently than weekly.

The Cancer Therapy Evaluation Program of the National Cancer Institute has developed a monitoring plan to better quantify the risk of AML after epipodophyllotoxin treatment. Smith and colleagues[106] reported results for patients included in trials that used epipodophyllotoxins at low (less than 1.5 g/m^2), moderate (1.5 to 2.9 g/m^2), or higher (3 g/m^2 or more) cumulative etoposide doses. The 6-year cumulative risks for AML (including MDS) with the low, moderate, and higher cumulative dose groups were 3.3% (based on eight AML cases in 451 patients), 0.7% (based on four AML cases in 1270 patients), and 2.2% (based on five AML cases in 570 patients), respectively. This result does not appear to provide support for a cumulative-dose effect for the leukemogenic activity of the epipodophyllotoxins, at least not within the cumulative-dose range and with the treatment schedules encompassed by the monitoring plan (cumulative etoposide dose of 5.0 g/m^2 or less, on daily times 2- to 5 schedules). A limitation of this study, however, is that the three treatment strata according to cumulative etoposide dose also differed with respect to other cytotoxic drugs received, primary tumor, and age. These differences and the administration of radiotherapy were not accounted for in the analysis.[93] Smith and associates[106] suggested that the much larger AML risk observed in earlier investigations might be due to the higher cumulative epipodophyllotoxin doses used in those studies (as high as 9 to 19 g/m^2)[97,234,235] or, alternatively, to their schedule of weekly or twice-weekly administration. This intermittent exposure schedule, which is not commonly used in current treatment regimens, has been associated with increased leukemogenicity *in vitro*.[237] In view of several inconsistencies between the studies conducted to date, final conclusions regarding the leukemogenicity of different epipodophyllotoxin-based regimens cannot yet be drawn.

Hawkins and associates[61] addressed the quantitative relationship between radiation dose, alkylating agent therapy, and risk of bone sarcoma in a case-control study within a British cohort of 13,175 3-year survivors of childhood cancer. Risk of bone cancer was strongly increased in all follow-up intervals beyond 3 years, with no apparent trend of increasing or decreasing relative risks up to 25 years after diagnosis of primary cancer. As in an earlier study,[19] no increased risk was observed for radiation doses to the site of the bone tumor of less than 10 Gy. At more than 10 Gy, risk for bone sarcoma rose sharply with increasing radiation dose, with a relative risk of 93 for patients who received 30 to 50 Gy as compared to those not treated with radiation. At higher radiation doses, however, the risk appeared to decline somewhat (Table 55.7-7). Such a downturn in relative risk at very high doses was also observed in a smaller case-control study of osteosarcoma after childhood cancer[238] but was not found in the large case-control investigation nested in the LESG cohort.[19] In the latter study, Tucker and colleagues[19] showed that the pattern of risk increase in relation to radiation dose was similar in patients treated for retinoblastoma and those treated for other initial malignancies. Thus, although patients with retinoblastoma have a higher intrinsic risk for sarcoma development, their relative responses to radiation treatment do not appear to be different from patients with other childhood cancers. Importantly, the study by Hawkins and colleagues[61] also showed that the relative risk of bone sarcoma increases with increasing cumulative exposure to alkylating agents, even after adjustment for radiation therapy (see Table 55.7-7). It is clear, however, that the effect of radiotherapy on sarcoma risk is stronger than that of chemotherapy. An association between chemotherapy and risk of bone sarcoma also has been observed in other studies[19,91,238,239]; an effect of alkylating chemotherapy on sarcoma risk in the absence of radiotherapy was found only in the LESG study.[19] Comparative studies of children and adults irradiated for Hodgkin's disease have shown that children experience a much higher relative risk of developing bone sarcomas than adults, probably because of greater radiosensitivity of growing bone.[12,62]

The risk of thyroid cancer after radiotherapy for childhood malignancies was assessed in the LESG cohort.[60] High relative risks compared with general population rates were observed for thyroid malignancies after treatment of neuroblastoma (RR, 350), Wilms' tumor (RR, 132), and Hodgkin's disease (RR, 67). The relative risk increased significantly with time since treatment throughout the observation period (more than 20 years). In a case-control study, radiation dose to the thyroid was estimated for 23 thyroid cancer cases and 89 matched controls. Radiation doses of 2 Gy or more carried 13 times greater risk than doses of less than 2 Gy ($P<.05$). Because all patients with thyroid cancer had been exposed to at least 1 Gy of radiation to the thyroid, the risk associated with doses less than 2 Gy could not be reliably determined in this study. However, the investigators estimated that the risk associated with doses of 2 Gy or more was increased approximately 130-fold compared to nonirradiated patients.[60] Unexpectedly, the dose-response relationship was more or less flat at radiation doses beyond 2 Gy; even at doses as high as 60 Gy, no decrease in thyroid cancer risk was observed. A pooled analysis of seven large studies of thyroid cancer after various radiation exposures demonstrated that the risk decreases significantly with increasing age at exposure and is highest for persons with radiation exposure before age 5 years.[59]

In conclusion, survivors of childhood cancer are at substantially elevated risk to develop new malignancies. The magnitude of this risk depends on the type of the initial malignancy, because some childhood cancers, such as bilateral retinoblastoma, carry a high intrinsic risk for second cancer occurrence. Long-term survival after various types of childhood cancer has become possible through therapies introduced from the early 1970s onwards. Consequently, the growing population of cured patients is just beginning to enter the ages at which adult cancers typically occur, so the full spectrum of second malignancies has not yet been encountered. It is therefore imperative that survivors of childhood cancer be carefully monitored to assess the long-term risks of various types of second cancers. Bone sarcoma has consistently been identified as the second malignancy for which the excess risk is highest. Of much interest is the potential interaction between genetic susceptibility and treatment in second cancer development. The leukemogenic potential of epipodophyllotoxin-containing regimens that vary in cumulative dose and schedule of administration should continue to be rigorously assessed. As quantitative risk information from more studies becomes available, it will be possible to carefully weigh the benefits derived from epipodophyllotoxin treatment against the risks. Second cancers among survivors of childhood cancer are associated with a poor prognosis.[97,230,232,240,241] Hence, the need is pressing to develop therapeutic strategies with less oncogenic potential, without compromising the excellent cure rates that have been achieved.

CONCLUSION

The results described in this chapter have multiple clinical implications. Knowledge of risk factors for second malignancy has made it possible to identify patient groups at high risk of developing second cancers due to treatments that they received in the past. Whenever effective screening methods are available, these should be implemented in the patients' follow-up program to improve their survival after diagnosis of second malignancy. In some cases, preventive strategies (e.g., smoking cessation) may reduce substantially the risk of developing a treatment-related cancer. The issue of treatment-induced second cancers must always be viewed in relation to the sometimes dramatic improvement in survival rates for patients with various malignancies. The risks associated with various treatments should be weighed carefully against the consequences of not using such treatments. Clinical research should focus on the development of therapeutic regimens with less carcinogenic potential. However, the arbitrary alteration of a successful therapy to mitigate second cancer risk is unwarranted. It is of the utmost importance that changes in therapy to reduce the risk of late complications be made only in the context of carefully designed clinical trials that evaluate whether the overall efficacy of treatment is maintained.

For many cancer treatments, the long-term effects on second malignancy risk are not yet known. In addition, new therapies are being introduced continuously, and the associated risks of late sequelae must be evaluated. Whenever possible, future studies of second cancer risk should incorporate investigations at the molecular level. Results of these laboratory analyses may clarify the influence of genetic susceptibility on treatment-related risk and contribute important data for the elucidation of mechanisms underlying drug- and radiation-induced carcinogenesis.

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SECTION **8**

RAYMOND B. WEISS

Miscellaneous Toxicities

NEUROTOXICITY

VINCRISTINE, VINBLASTINE, AND VINORELBINE

The first drug class to be recognized as having neurotoxicity was the vinca alkaloids, especially vincristine. Vincristine is unique among the antitumor agents in that neurotoxicity is the sole dose-limiting problem. The neurologic injury can occur in the peripheral, central, or autonomic nervous systems.[1,2]

The most common and initial manifestations of neurotoxicity are depression of the deep tendon reflexes and paresthesias of the distal extremities. The Achilles' tendon reflexes and the fingertips are the usual respective initial sites of abnormalities. Loss of the tendon reflexes is usually asymptomatic. The paresthesias commonly progress proximally as vincristine therapy is continued and may involve the entire hands or feet. Despite the presence of peripheral paresthesias, vibration sense, position sense, pinprick sensation, and two-point discrimination are generally unaffected.

Motor dysfunction and gait disorders are initially manifested as lower extremity weakness. Footdrop may ensue, and if vincristine is continued, weakness to the point of paraparesis may develop. However, when vincristine and corticosteroids are administered together, steroid myopathy often occurs and causes similar symptoms of weakness, which should not be ascribed to vincristine neurotoxicity and result in a dose modification of the wrong drug.[3] Patients with hereditary neuropathies are especially prone to the additive effects of vincristine neuropathy.[4] Severe bone pain (especially in the mandible) may occur acutely a few hours after drug administration but usually subsides after a few days.[5]

Cranial nerves may be affected and cause ophthalmoplegia and facial palsy. Toxicity to the parasympathetic nervous system is manifested by constipation and difficult micturition, which can progress to paralytic ileus and bladder atony. Autonomic neuropathy can produce orthostatic hypotension (which can be symptomatic or clinically silent[6]) and erection/ejaculatory dysfunction.[7] Other rare, but severe, neurotoxic manifestations observed from vincristine include cortical blindness[8] and laryngeal nerve (with vocal cord) paralysis,[9] resulting in dysphonia and even aphonia.

Neurotoxicity from the vinca alkaloids, especially vincristine, is both an individual dose and a cumulative dose phenomena. The usual practice in adults is to limit an individual dose of vincristine to 2 mg. Studies of higher vincristine dosing[7] have shown a very high rate of neurotoxicity. No effective prevention or treatment has been developed except to stop therapy and wait for neurologic recovery. The neuropathy symptoms may persist as long as 3 or 4 years after cessation of therapy, but they usually wane to a point where they are no longer troublesome to the patient.[10] Empiric vitamin therapy is ineffective. Intestinal dysfunction from autonomic neuropathy may be improved by metoclopramide therapy.[11]

Vincristine binds to the B subunit of tubulin, causing disruption of microtubule function in neuronal axons. Electrophysiologic studies indicate distal axonal dysfunction, and nerve conduction testing shows sensory nerves are most affected with a reduced amplitude of nerve action potentials. Histologic changes are generally those of axonal degeneration.

The vincristine analogues vinblastine and vinorelbine also have neurotoxicity potential. The primary dose-limiting toxicity of both vinblastine and vinorelbine is myelosuppression, and neurotoxicity is less common than that occurring from vincristine. The form and range of neurotoxicity manifestations from these analogues are similar to those of vincristine, and again, the degree of dysfunction is related to both individual and cumulative drug doses. However, vinblastine and vinorelbine seem to produce more autonomic effects, resulting in severe constipation and paralytic ileus.[12]

Concurrent use of two neurotoxic agents has been reported to cause enhanced neurotoxicity or no such toxicity, depending on the drug involved. The combination of vinorelbine and cisplatin seems not to increase the incidence or severity of neuropathy.[13] However, when vinorelbine is used either in combination with, or sequentially after, paclitaxel, there is more potential for severe neuropathy.[14,15] In addition, the combination of vincristine and a granulocyte growth factor may precipitate a severe neuropathy involving primarily the legs.[16]